Organic Chemistry

Second Edition

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Preface

Since the publication of the first edition of *Organic Chemistry* in 1935, important changes have taken place in the field of organic chemistry. The teaching of the subject has so changed that the innovations of that time have now become standard teaching practice, and underlying theory has been greatly enriched by numerous studies and investigations. Moreover, many new reactions and a very large number of new organic compounds have been discovered. Thus the beginning student is confronted with a greatly increased wealth of information. One purpose of this edition is to meet the problems connected with an ever-expanding field by emphasizing some fundamental principles, so that the student will be better able to grasp and understand the general relationships governing physical properties and chemical reactions of organic compounds.

In line with this purpose, Chapters 2 and 3 deal with the fundamental concepts of energy relationships, resonance, dipole moments, ionic character in covalent bonds, and relative electronegativities of atoms and radicals. Application of these concepts is made throughout the text to explain phenomena and to compare, correlate, or contrast the properties and reactions of different types of compounds. In this connection some attention is devoted to reaction mechanism. Also, emphasis has been placed on class reactions rather than on the reactions of individual compounds; and physical data have, in the main, been arranged in tables to show the relationship between each compound and other members of its class. The problems at the ends of the chapters have been designed to test the student's mastery of general principles.

During recent years new areas of applied organic chemistry have been opened—for example, the sulfa drugs, synthetic detergents, synthetic rubber, synthetic motor fuels, and high polymers. Although the space given to these developments must necessarily be limited, some emphasis has been placed upon the underlying features of the chemistry connected with the different fields.

From the standpoint of instruction there are advantages to the order of topics: early description of cycloalkanes and of the strain theory of rings, so as to apply this theory to other types of compounds; early differentiation between intermolecular and intramolecular reactions, and its significance in connection with polymeric reactions; early treatment of organometallic

compounds, thus permitting their use throughout most of the text; simultaneous description of ethers, esters, anhydrides, and acyl halides so as to emphasize their similarities and differences; and separate treatment of aromatic hydrocarbons, so as to emphasize aromatic substitution.

The author takes this opportunity to thank a number of his colleagues for criticisms and suggestions in connection with the revision; Drs. Albert L. Henne and Harry Walborsky, for reading most of the manuscript; Dr. Linus Pauling, for help with Chapters 2, 3, and 41; Drs. David Pressman, John D. Roberts, and Verner Schomaker, for help and criticism of Chapters 2 and 3; and Dr. Oliver R. Wulf for criticism of Chapter 46.

Contents

CHAPTER 1

Introduction

Definition. Organic Chemistry deals with the chemistry of the compounds of carbon. Carbon is a constituent of all living matter and is present in the substances which are elaborated in the cells of plants or produced in those of animals.

At one time, somewhat more than one hundred years ago, chemists distinguished two kinds of matter, mineral or inorganic on the one hand and organic on the other. Organic substances were those which had been produced in living organisms, either vegetable or animal, or could be obtained from such by chemical reactions, while inorganic compounds were those occurring as such in minerals or obtainable from them by chemical means. Thus rock salt, marble, soda, carbon dioxide, etc., were inorganic, whereas acetic acid (from vinegar), alcohol (from wine), tartaric acid (from grapes), etc., were organic. In those days it was not possible to prepare organic compounds from inorganic substances. It was thought that a mysterious "vital force" was necessary and that this force resided only in living matter. The laboratory production of organic material out of inorganic substances was regarded as impossible of attainment. But Wohler in 1828 by obtaining urea from ammonium sulfate and potassium cyanate showed that the artificial production of organic matter is possible. Since that date, which is generally regarded as the beginning of modern organic chemistry, the passage of time has witnessed the synthesis of thousands of naturally occurring "organic" substances. It is thus evident that the term *organic* no longer retains its original significance. The chemist classifies under this head all of the compounds of carbon except those having a mineral origin.

Sources. Compounds of carbon are obtained from natural sources and by artificial means. As a manufacturer of many substances, nature has not been excelled. Man still finds it preferable to utilize plants and animals for the production of a large variety of materials, either because synthesis of the material has not been realized or because the natural source is more economical. Some important plant products are sugars, starches, fats, proteins, turpentine, quinine, and strychnine; some important animal products are fats, proteins, adrenalin, and thyroxine.

The pyrogenic decomposition of coal produces a mixture of carbon compounds called coal tar, from which a host of other compounds can be made. Other organic materials, such as wood and bones, also yield mixtures of carbon compounds when subjected to similar treatment. Petroleum is another complex mixture of carbon compounds which in general is an alteration product of organic matter laid down in the earth's crust in past ages. By synthetic methods the organic chemist has built up not only a large number of compounds occurring in plants and animals but also thousands of others which have no connection with living organisms. To this group, which are strictly synthetic products, belong most of the dyes, many useful drugs, and hosts of other substances.

Reasons for Separate Study. Organic chemistry is amply entitled to separate study because of the large number of characteristic reactions of organic compounds and the systematic way in which compounds can be classified in terms of chemical behavior. This classification greatly simplifies the study of the very large number of known compounds. Indeed, it even is possible to predict the reactions of compounds not yet known.

Carbon is unique among elements in the ability to form complicated molecules in which large numbers of like atoms are joined to one another. In hexacontane, $C_{60}H_{122}$, sixty carbon atoms are joined together in a stable molecule. Since carbon is quadrivalent, it can be attached to as many as four other carbon atoms. The number of permutations possible with carbon and hydrogen is enormous (see Table 18, p. 48). The possibilities are greatly increased when an atom of some other element, as for example oxygen or nitrogen, is present in the molecule.

The number of known carbon compounds in 1950 has been estimated at various figures mostly above 500,000, some as high as 1,000,000. Some idea of the way organic chemistry grows is shown by Table 1, which gives the number of known compounds in different years.

TABLE 1 | Number of Known Carbon Compounds

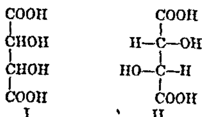
Year	1902	1910	1920	1930	1950
Number	100,000	145,000	200,000	300,000	630,000

The 1902 value of 100,000 and the 1910 value of 145,000 were compiled from Richter's *Lexikon der Kohlenstoff Verbindungen.* The 1920, 1930, and 1950 values of 200,000, 300,000, and 630,000, respectively, are approximate. Of the last, about 30,000 are naturally occurring and about 600,000 are synthetic. The number of known compounds of all the other elements is about 30,000 The last four figures have been kindly supplied by Dr. E. J. Crane, Editor of *Chemical Abstracts,* who estimates also that about 30,000 new organic compounds are announced each year.

Classification of Organic Compounds. The beginner should not be discouraged by the immensity of the number of compounds. Fortunately the study of organic chemistry is simplified by classification into types (classes) of compounds, as for example, hydrocarbons, alcohols, acids, esters, etc. The compounds of a given type or class resemble one another in that they react similarly, because of the possession of the same **functional group.** This is a like grouping of atoms, as for example the hydroxyl group in alcohols. A given functional group generally undergoes the same reactions, whether in small or large molecules. Thus the study of organic chemistry is mainly the study of the reactions of different functional groups, or in other words, the general reactions of different classes of organic compounds. It is even possible for an organic compound to exhibit the reactions of two or more classes, owing to the presence of two or more functional groups in the molecule.

Determination of Structure. Although the reactions of a given compound depend upon the number and kind of functional groups present, this does not necessarily establish the structure, since isomeric forms (resulting from different arrangements of the atoms in the molecule) may be possible. Thus an important function of organic chemistry is the determination of structures, especially of naturally occurring substances. The steps involve the determination of: (1) the **empirical formula,** from the elementary analysis; (2) the **molecular formula,** from elementary analysis and molecular weight determination; (3) functional groups, from a study of class reactions; (4) the **structural formula,** by degradation and synthesis; and (5) **stereochemical formula,** by special means.

Tartaric acid is a good example. From elementary analysis (C, 40.66%; H, 5.12%) the empirical formula is $C_2H_3O_3$, and from molecular weight determinations the molecular formula is $C_4H_6O_6$. From chemical reactions there are found to be four functional groups in the molecule, *viz.*, two alcoholic hydroxyl groups (OH), and two carboxyl groups (COOH). Further investigations show that these groups are arranged in the molecule according to the structural formula, I, below. The spatial arrangement of the groups, as shown by II, is the final stereochemical formula.



The empirical formula is the simplest formula showing the relative number of atoms of the different elements in the molecule. The molecular formula is the number of atoms of the different elements in the molecule. It may be the same as the empirical formula, or some multiple of it. The structural formula shows how the different atoms are joined to one another, and the

stereochemical formula shows how the atoms are arranged in space. In a great many cases there is no difference between the structural and the stereochemical formulas.

Value of Organic Chemistry. The importance of organic substances and of their reactions is evident in everyday life. Most important of all is the process of life itself. Man's body is a very complicated and highly organized arrangement of thousands of different carbon compounds. His food is organic. The processes of digestion bring about the decomposition of foods (sugars, starches, fats, protein) to simpler organic compounds, while the utilization of these latter in the animal body and their conversion to needed materials are reactions involving changes to other organic compounds. In addition, many other substances used by man are carbon compounds; for example, fuels (coal, wood, petroleum, natural gas, gasoline), clothing (cotton, wool, linen, rayon), dyes, explosives, drugs, anesthetics, antiseptics, photographic developers, perfumes, waxes, lacquers, etc.

A knowledge of organic chemistry is valuable to the biologist and manufacturer, as well as to the chemist, since organic chemistry is important in the fields which have to do with any process which involves an organic substance. It is obvious that an understanding of the chemical changes going on in plants and animals must rest upon a foundation of organic chemistry. Progress in organic chemistry research and in the industrial production of organic compounds requires a good training in the subject. As the field of organic chemistry expands, continued improvement is witnessed in the production of compounds with new and superior properties, in methods of production, and in finding new uses for known compounds.

PROBLEMS

1. What is the empirical formula of a compound which has the percentage composition given below (note that usually analyses are not made for oxygen; its percentage is calculated by difference). On the basis of the usual valence of the elements, determined by their positions in the periodic table, construct a reasonable structural formula for the compound, if necessary assuming a molecular formula different from the empirical formula.

a) C, 85.6%; H, 14.4%
b) C, 82.7%; H, 17.3%
c) C, 84.2%; H, 15.8%
d) C, 64.7%; H, 13.6%
e) C, 26.7%; H, 2.2%
f) C, 73.8%; H, 13.9%
g) C, 65.8%; H, 15.1%; N, 19.1%
h) C, 39.3%; H, 11.5%; N, 23.0%
i) C, 29.9%; H, 6.2%; Cl, 44.0%
j) C, 18.7%; H, 1.5%; Cl, 55.0%

CHAPTER 2

Chemical Bonds

Chemical bonds are the forces that hold atoms together in molecules. An attractive force between two atoms which can be broken by the absorption of less than 20 kcal. of energy per mole usually is not considered a chemical bond. Chemical bonds between atoms can be formed either by a transference of one or more electrons from one atom to another, with resultant attractive force between two charged particles, or by a sharing of electrons. In organic chemistry the bonds of principal interest are limited to those between elements of the first two rows of the periodic table (plus the rest of the halogens).

TABLE 2 | **Electron Arrangement of the Lower Elements** [a]

(1)·							·(2)·
·(3)··	··(4)··	··(5)··	··(6)··	··(7)·:	:·(8)·:	:·(9)·:	:·(10)·:
:·(11)·:·	·:·(12)·:·	·:·(13)·:·	·:·(14)·:·	·:·(15)·::	::·(16)·::	::·(17)·::	::·(18)·::

[a] The circles represent the nuclei, which carry positive charges as indicated; the dots represent the electrons outside the nuclei.

Atomic Structure. In Table 2 are shown the structures of the lower elements in terms of positive nuclei (circles) and negative electrons (dots). Although for simplicity the electrons are shown as stationary, the reader should understand that the electrons are moving very rapidly and that the dots are merely representations of average positions, also, that the relative positions represent different energy levels or shells. The electrons closest to the nucleus, the K electrons, have the lowest energies, that is, they are in the

most stable state, those next, the L electrons, have higher energies, etc. It should be understood also that in general two electrons should not be represented singly, for usually they are paired. This pairing is the result of their having opposite spins.

Hydrogen (at. no. 1) has one K electron and helium (at. no. 2) has two. Only two electrons can occupy the K shell. In the lithium atom (at. no. 3) two electrons are in the K shell and one is in the L shell. With increasing atomic weight additional electrons are added to the L shell until, in the neon atom (at. no. 10), there are eight electrons in this shell. *There can never be more than eight electrons in the L shell.* This statement is important in connection with the structure of molecules.

Sodium (at. no. 11) has two K electrons, eight L electrons, and one M electron. In passing from sodium to argon (at. no. 18), electrons are added to the M shell until the argon atom, like the neon atom, has eight electrons in the outer shell (the M shell) as well as eight in the L shell and two in the K shell. Usually the maximum number of electrons in the M shell of second row elements is eight, although there are exceptions in which the octet is expanded, as when an atom is combined with a number of atoms of a strongly electronegative element. Examples are phosphorus pentafluoride and sulfur hexafluoride. In the atoms of most elements above argon the M shell has more than eight electrons.

The periodicity of the electron arrangements in the outermost shells is of great importance. Lithium and sodium, likewise potassium, rubidium, and cesium, have one electron in the outer shell, beryllium and magnesium two, boron and aluminum three, carbon and silicon four, etc. These outer electrons determine the chemical properties of the elements and are, on that account, often referred to as the **valence electrons.** The atom **within the valence shell,** *i.e.*, the nucleus and the inner electrons, is called the **kernel.** The advantage of this method of nomenclature is shown in Table 3, where the kernel of an element is represented by the usual symbol of that element and the valence electrons are represented by dots.

TABLE 3 | Valence Electrons and Kernels of the Lower Elements

KERNEL CHARGE	1	2	3	4	5	6	7	0
	H·							·He·
	Li·	·Be·	·Ḃ·	·Ċ·	·Ṅ:	:Ö:	:F̈:	:N̈e:
	Na	·Mg·	·Ȧl·	·Ṡi·	·Ṗ:	:S̈:	:C̈l:	:Är:

The similarity of elements in the same column is well shown in Table 3. If other elements were added, it would be noted that all alkali metals, including

potassium, rubidium, and cesium, have only one electron in the valence shell, and all halogens, including bromine and iodine, have seven. Thus the number of valence electrons of the lighter (lower) atoms and of some of the heavier ones is the same as the position of the element in the periodic table. This generalization does not hold for many of the heavier elements because of the *ability of an inner shell, M or N, to take on additional electrons.*

In the modification of the original Mendeleeff Table (Table 4) the relationship of the higher elements to those of the first two rows is shown by the rela-

TABLE 4 | The Periodic System of the Elements (1951)

	H 1	He 2

0	I	II	III	IV	V	VI	VII	0
He 2	Li 3	Be 4	B 5	C 6	N 7	O 8	F 9	Ne 10
Ne 10	Na 11	Mg 12	Al 13	Si 14	P 15	S 16	Cl 17	A 18

0	Ia	IIa	IIIa	IVa	Va	VIa	VIIa	VIII			Ib	IIb	IIIb	IVb	Vb	VIb	VIIb	0
A 18	K 19	Ca 20	Sc 21	Ti 22	V 23	Cr 24	Mn 25	Fe 26	Co 27	Ni 28	Cu 29	Zn 30	Ga 31	Ge 32	As 33	Se 34	Br 35	Kr 36
Kr 36	Rb 37	Sr 38	Y 39	Zr 40	Nb 41	Mo 42	Tc 43	Ru 44	Rh 45	Pd 46	Ag 47	Cd 48	In 49	Sn 50	Sb 51	Te 52	I 53	Xe 54
Xe 54	Cs 55	Ba 56	La 57 *	Hf 72	Ta 73	W 74	Re 75	Os 76	Ir 77	Pt 78	Au 79	Hg 80	Tl 81	Pb 82	Bi 83	Po 84	At 85	Rn 86
Rn 86	Fr 87	Ra 88	Ac 89 *‡	Th 90	Pa 91	U 92												

* Rare-earth metals	Ce 58	Pr 59	Nd 60	Pm 61	Sm 62	Eu 63	Gd 64	Tb 65	Dy 66	Ho 67	Er 68	Tm 69	Yb 70	Lu 71
‡ Uranium metals	Th 90	Pa 91	U 92	Np 93	Pu 94	Am 95	Cm 96	Bk 97	Cf 98					

tive width of the bands connecting them to the lighter elements. Thus subgroup I*a* is more like I than is I*b*, subgroup VII*b* is more like VII than is VII*a*, etc. Of two subgroups, the one closer to the noble gases is the one which more closely resembles the elements of the first two periods.

Ionization Potentials. When a gaseous atom is subjected to bombardment by a stream of electrons, the energy which the electron stream must

possess in order to knock an electron out of the atom is called the ionization potential of the element, for the atom is converted into a positive ion. The potential is given in terms of electron volts. Figure 1 shows the ionization potentials of the lower elements, when the atom, by loss of one electron, is converted into a unipositive ion.

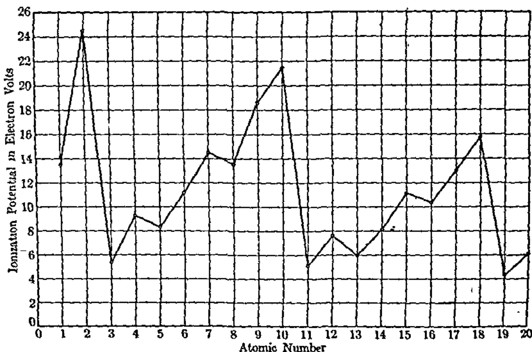


Figure 1 • Ionization Potentials of the Lower Elements

It is noted that alkali metals have the lowest ionization potentials and the noble gases have the highest. The halogens are next highest. In general, the ionization potential increases in going across the periodic table and decreases in going down the table. The general relationships shown in Figure 1 are true also in a chemical sense, for alkali metals are the elements which most easily are converted to positive ions and the noble gases those least easily, followed by the halogens.

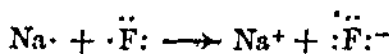
The ionization potentials of positive ions must be considered when discussing the formation of gaseous bipositive ions by removal of a second electron. These potentials, which are of the same order of magnitude as the first so long as the two electrons are in the same shell, indicate that the formation of a bipositive ion requires the absorption of more energy than that of a unipositive ion. It is evident, therefore, that tripositive ions require still more energy, and so on.

Electron Affinity. This is a measure of the tendency of a neutral gaseous atom to take on an electron, to form a negative ion. Fluorine has the highest electron affinity. Chlorine and oxygen also have high values. The alkali metals and the noble gases seem to have no affinity for electrons. Thus

oxygen and the lighter halogens, those which usually are regarded as the strongest nonmetallic elements, are especially noted for their strong tendencies to acquire electrons.

Bond Formation. The two characteristically stable electron arrangements are the pair and the octet. The chemical properties of elements of main interest to the organic chemist, elements in the first two rows of the periodic table, can be summarized in the statement, an atom tends to acquire the electron configuration of one of the noble gases; namely, helium, neon, or argon. A nonmetallic element gains one to four (sometimes even more), and a metallic element loses one to three electrons. (It should be noted that quadripositive ions are rare).

Electron Transfer. This takes place only if one element has a relatively low ionization potential. The products are salts composed of positive metal ions and negative nonmetal ions, for example, lithium chloride, sodium fluoride, potassium iodide, calcium oxide, etc. In sodium fluoride, for example, the ions of both elements have the neon structure, fluorine by the gain of an electron, sodium by the loss of an electron, as shown in the equation below.



In Figure 2 the ions are written to show their relationship to the neon atom. It is seen that they are alike as regards the number and arrangement of elec-

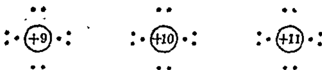
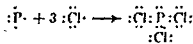


Figure 2 • Similarity in Structure of Fluoride Ion, Neon Atom, and Sodium Ion

trons and differ in the magnitude of the kernel charge. In solid sodium fluoride the force holding the ions together in the crystal lattice is electrostatic in character. Valence of this sort often is called **electrovalence**, and the bond an **electrostatic, or ionic, bond.** Strictly speaking, this is an oversimplification but is satisfactory for this discussion. Actually, in a crystal lattice of the sodium chloride type, where each sodium ion is equidistant from six chloride ions, and *vice versa*, there are six weak bonds to each ion.

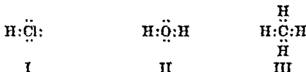
Electron Sharing. When a compound is formed from two elements, neither of which has a low ionization potential, and both of which have strong tendencies to acquire electrons, the phenomenon of electron sharing takes place. Since the atom of neither element easily loses electrons, one or more pairs must be held in common in order for the atoms of each element to complete their octets. The formation of phosphorus trichloride from the elementary forms of phosphorus and chlorine is a good example.



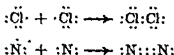
Thus each chlorine atom completes its octet by sharing one electron pair with the phosphorus atom, and the latter completes its octet by sharing three electron pairs with three chlorine atoms. Each atom contributes one electron to the bond.

This is the **shared-electron bond (electron-pair bond)** proposed by G. N. Lewis in 1916. Sometimes it is called a **covalent bond,** or a **covalency.** The covalent bond, therefore, is a shared-electron bond between two atoms, both of which contribute the same number of electrons to the bond. The shared-electron bond is important in organic chemistry, because most bonds involving carbon are of this type. Many complex inorganic ions, for example, sulfate and nitrate ions, also contain electron-pair bonds.

Number of Shared Electrons Between Octets. In compounds where only one atom has a complete octet, as in water, H_2O, ammonia, NH_3, methane, CH_4, etc., it is evident that the valence electrons supplied by all of the atoms total eight, the number required to complete the octet of the heavier atom. In order to write the electronic structure of the molecule it is necessary only to attach a hydrogen nucleus to an electron pair, as in hydrogen chloride, I, water, II, and methane, III.

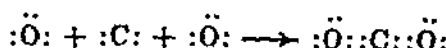


In molecules where two octets are completed by electron sharing, the number shared is two when both atoms have seven valence electrons and six when they have five (oxygen is unusual in having three-electron bonds).



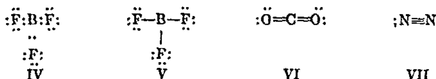
Each chlorine atom contributes one electron to the bond and each nitrogen contributes three.

In triatomic and more complicated molecules the number shared is sufficient to give complete octets to the various atoms with the exception of hydrogen (associated with a pair) and a few other elements (boron, for example, may have only six electrons, as in boron trifluoride, IV). In carbon dioxide, for example, where carbon has four and oxygen six electrons, octets are completed by the sharing of four electrons between carbon and each oxygen atom.



It is thus possible to construct the electronic formulas of molecules by starting with the atoms and their normal quota of valence electrons. It is possible also to construct electronic formulas of ions, for example, nitrate ion. In such cases the charge on the ion must be taken into account.

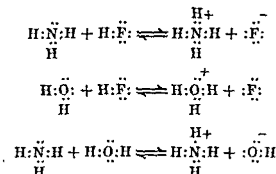
Electronic formulas may be written so as to show either all of the valence electrons in the molecule, or else only the unshared valence electrons and lines to represent the shared-electron bonds. A single line is drawn for one shared-electron pair, two lines for two pairs and three lines for three pairs. Typical formulas are those for boron trifluoride, V, carbon dioxide, VI, and nitrogen, VII.



Usually the number of electrons shared between two nuclei is even, *i.e.*, two, four, or six. Two electrons constituted a single bond, four electrons a double bond, and six electrons a triple bond. The commonest bonds are single bonds. The double bond is present in many compounds of first row elements, but is less common in compounds of higher elements. The triple bond is rare except for first row elements.

First row elements never have more than eight electrons in the valence shell. This is known as the **octet rule.** Second row elements seldom have more than eight electrons in the valence shell.

Proton Transfer. When hydrogen is attached to a strongly electronegative element like the halogens, it tends to leave this atom and become attached to an unshared electron pair of an atom of smaller kernel charge. In first row elements the tendency to leave an electronegative atom is in the order: F > O > N > C. The reactions are reversible.



The first reaction usually is regarded as a neutralization reaction, for ammonia acts as a base. The second reaction also could be regarded as the neutralization of hydrogen fluoride by water, and in a sense this is correct, for the acidity of aqueous hydrofluoric acid is lower than that of anhydrous hydrofluoric acid. The reaction also can be regarded as the ionization of hydrogen fluoride when it is dissolved in water. The third reaction, by analogy, could be regarded as the neutralization of the very weak acid, water, by the base, ammonia. The reactions are all reversible, the first one least, the last most.

The Hydrogen (Proton) Bond. One of the best examples of the hydrogen bond is found in solid potassium bifluoride, KHF_2. This has been studied

*by X-ray diffraction methods and has been found to consist of positive potas*sium ion and negative bifluoride ion, HF_2^- The fluorine atoms occur in pairs in which the fluorine-to-fluorine distance is 2.36 A, considerably less than twice 1.36 Å, the crystal radius of fluoride ion. This is explained on the basis that attraction of two negative fluoride ions for the positive hydrogen nucleus draws the two negative ions closer together.

The tendency of a proton to form a bond is greatest when it is attached to fluorine, and decreases in the order: $F > O > N > C$; and $F \gg Cl, Br, I$. The tendency of an unshared electron pair to accept a proton, either by transfer or by hydrogen bond formation usually increases in the order: $F < O < N$. Hydrogen bond formation is important in connection with dielectric constants and association (p 32).

Formal Charges. It is possible to assign a formal charge to each atom in a molecule by subtracting from its kernel charge the sum of the charges of the electrons in its valence shell. This sum equals the number of unshared electrons in the valence shell plus one half the number of electrons shared equally with other atoms. For example, the formal charge on the nitrogen atom is 0 in ammonia, VIII, and +1 in ammonium ion, IX.

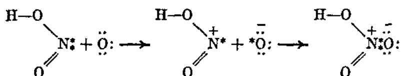
```
                     H +
   ..                ..
 H N·H             H:N:H
   ..                ..
   H                 H
  VIII               IX
```

The formal positive charge of the nitrogen atom in IX is balanced by the negative charge of the anion.

Historically and for many decades before the development of the electronic theory of valence, nitric acid was written with pentavalent nitrogen, each oxygen atom doubly bonded to the nitrogen atom, X.

```
H—O           H—Ö:              H—O            H—O
   \             .·+ ‒             \+  ‒          \
    N=O           N:Ö:              N—O            N→O
   //            .·  ..            //             //
  O            :O                 O              O
  X             ..XI              XII            XIII
```

But because nitrogen cannot have more than eight electrons in its valence shell, the correct structure of the acid is XI. When formal charges are assigned to the atoms, it is seen that the nitrogen atom carries a positive charge and the oxygen a negative charge, XI and XII. The bond between these two atoms is a combination of a covalency (the shared pair) and of an electrovalency (the charges). Thus it is a sort of double bond, made up of one shared-electron bond and one ionic bond. Some chemists still prefer to think of it as being formed by stages, in the way it was originally postulated by Sidgwick, through the actual transfer of an electron from the nitrogen atom of nitrous acid to an oxygen atom, analogous to the reaction of sodium and fluorine to form positive sodium ion and negative fluoride ion.



Here the electrons of the nitrogen atom are shown by asterisks Thus the first stage results in the formation of an electrostatic bond, and the second stage is the formation of a single covalent bond by each atom contributing one electron to the bond. The overall result is the same as when one calculates formal charges and indicates that the nitrogen atom contributes two electrons, the oxygen none, to form the bond. In formula XIII the arrow indicates that an electron moved originally from N to O, or that the nitrogen atom furnishes the two electrons for the bond. Thus, XI, XII, and XIII are equivalent. This type of bond sometimes is called a **semipolar double bond,** or **coordinate covalency.**

The semipolar double bond often is associated with nitrogen and is fairly common in organic chemistry. Also it is believed to be present in sulfuric acid, perchloric acid, and in many organic sulfur compounds containing also oxygen. In these molecules the sulfur or chlorine atom usually is written with an octet. The complete structure in these cases, however, may not be so simple, since these atoms sometimes can have more than eight electrons in the valence shell.

Bond Lengths and Bond Angles. The distance between the centers of two atoms in combination with each other is the bond length (bond distance, or interatomic distance) while the angle formed between the lines joining the center of one atom to the centers of two other atoms which are attached to it is the bond angle. A large number of interatomic distances and bond angles have been determined experimentally by such methods as X-ray diffraction by solids, electron diffraction by gases, and measurements of the infrared spectra of gases.

Covalent Radii. In covalent compounds the atoms may be regarded as spheres, and any two in combination may be regarded as touching each other. Then the bond length will be the sum of the radii of the two spheres. Generally the covalent radius of a given atom is a reasonably constant value, more or less independent of the atom to which it is joined. However, there may be some variation. The values for the hydrogen atom (Table 5, p. 14) show rather large deviations. In Table 5 are listed the covalent radii of the elements most likely to be present in organic compounds. The most important values to the organic chemist are those of carbon, nitrogen, oxygen, sulfur, and halogens.

Interatomic distance is shortened as the bond changes from single to double to triple. This is because the larger the number of electrons between atomic nuclei the greater is the force which draws them together. Although a double bond is roughly twice as strong as a single bond the interatomic distance is not halved, because the repulsion between nuclei increases rapidly as the

distance is shortened. For first row elements the length of the double bond is 87 per cent and that of the triple bond is 78 per cent of the corresponding single bond length.

TABLE 5 | **Normal Covalent Radii (in Ångstrom units [a])**

(Pauling, 1939)

ELEMENT	SINGLE BOND	DOUBLE BOND	TRIPLE BOND	ELEMENT	SINGLE BOND	DOUBLE BOND	TRIPLE BOND
H	0.30 [b]			Si	1.17	1.07	1.00
B	.88	0.76	0.68	P	1.10	1.00	0.93
C	.771	.665	.602	S	1.04	0.94	.87
N	.70	.60	.547	Cl	0.99	0.89	
O	.66	.55	.50	Br	1.14	1.04	
F	.64	.54		I	1.33	1.23	

[a] One Ångstrom unit is 10^{-8} cm.
[b] This varies from 0.28 Å in hydrogen fluoride to 0.37 Å in the hydrogen molecule.

Bond Angles. In Table 6 are shown bond angles for a number of compounds. It is important to note that in water, methyl ether, and hydrogen sulfide, the value of the bond angle shows that the molecule is not linear

TABLE 6 | **Bond Angles in Some Gaseous Molecules**

SUBSTANCE	FORMULA	BOND ANGLE	SUBSTANCE	FORMULA	BOND ANGLE
Water	H—O—H	105°	Methane	CH_4 (H, H, C, H, H)	109° 28′ (tetrahedral)
Methyl ether	CH_3—O—CH_3	111°	Ethylene	$H_2C{=}CH_2$ (β = H–C–H; α = H–C=C)	α = 124°, β = 112° (planar)
Hydrogen sulfide	H—S—H	92°	Methyl-acetylene	$H_3C\overset{\alpha}{-}C{\equiv}C$	α = 180° (linear)
Ammonia	H—N(H)—H	108° (pyramidal)	Methyl cyanide	$H_3C\overset{\alpha}{-}C{\equiv}N$	α = 180° (linear)
			Allene	$H_2C{=}\overset{\alpha}{C}{=}CH_2$	α = 180° (linear)

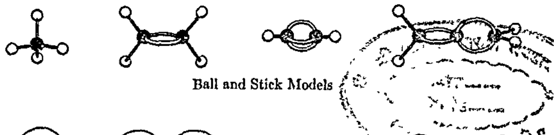
Also, neither ammonia nor methane is a planar molecule. The angle of 109° 28′ is of fundamental importance to organic chemistry. In the methane molecule the hydrogen atoms are located at the corners of a regular tetrahedron and the carbon atom at the center. The angle which each bond makes with the other three bonds is thus 109° 28′, the tetrahedral angle (Fig. 3). The tetrahedral arrangement of atoms or groups about a carbon atom, as in methane and numerous other organic compounds, was proposed as long ago as 1876 by van't Hoff and Le Bel and has been one of the axioms of organic chemistry since then.

In ethylene the angle β (Table 6) would be expected to be 109° 28′, since it is a tetrahedral angle, and thus the angle α would be 125° 16′. The observed values are close to the calculated ones. In methylacetylene and allene, α would be expected to be 180°, and has been found to have this value.

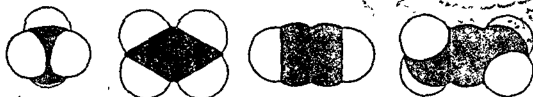
The space arrangement of the atoms is shown by tetrahedral models, as in Figure 3. In ethylene two carbon tetrahedra have an edge in common and



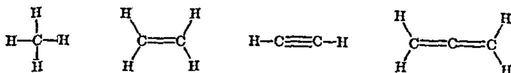
Tetrahedral Models



Ball and Stick Models



Hirschfelder Models



Projection Models

methane ethylene acetylene allene

Figure 3 • The Molecules of Methane, Ethylene, Acetylene, and Allene

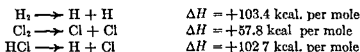
all six atoms of the molecule lie in a plane. In acetylene two carbon tetrahedra have a face in common and all four atoms are linear. In allene the middle carbon tetrahedron shares two edges, one with a second, the other with a third tetrahedron. All three carbon atoms are linear. The arrangement of the atoms in space is shown better by the ball and stick models and by the Hirschfelder models. The last named are constructed on the basis of atomic radii.

An interesting compound is nitrous oxide. Its molecule is linear. This is known from electron diffraction studies. The oxygen atom is not in the middle, XIV, because with eight shared electrons, the oxygen atom would carry a doubly positive charge. Since oxygen is more electronegative than nitrogen (see Fig. 5, The Electronegativity Map, p. 34), a form in which oxygen carries even a single positive charge would lead to decreased stability. Thus XIV is ruled out as a likely formula of nitrous oxide. This leaves XV, in which the middle atom is a nitrogen atom, as the only other structure for a linear molecule This is described in more detail under Resonance (p. 19).



Bond Energies. Bond energy is defined as the amount of energy that must be absorbed by one mole of a gaseous diatomic molecule in order to separate it into gaseous atoms, at 25° and one atmosphere pressure. Conversely, bond energy is the amount of energy liberated when one mole of the gaseous molecular species is formed by combination of the gaseous atomic species. The idea can be extended to bonds in triatomic and other more complicated molecules. Sometimes the bond energy can be determined experimentally by measuring the amount of energy necessary to cause rupture of the bond by electron impact or by radiation. More often, especially with organic compounds, it is calculated from the thermodynamic data, such as heats of formation and heats of combustion. **All bond energies are positive.** In Table 7 are the bond energies of a large number of covalent bonds.

All dissociation reactions absorb energy and are endothermic. If H is used to indicate the heat content of the system, it is evident that H, after reaction has taken place, is greater than H of the reactants, and that ΔH, the change in H, is positive, as a few examples show.



$$H_2 \longrightarrow H + H \qquad \Delta H = +103.4 \text{ kcal. per mole}$$
$$Cl_2 \longrightarrow Cl + Cl \qquad \Delta H = +57.8 \text{ kcal per mole}$$
$$HCl \longrightarrow H + Cl \qquad \Delta H = +102.7 \text{ kcal. per mole}$$

Although such reactions can be written, it is important to understand that they do not take place spontaneously, but only under conditions where energy is available. These could be very high temperatures, or bombardment at ordinary temperatures with energy-rich particles, for example, electrons or protons moving at high speed.

TABLE 7 · Some Common Bond Energy Values (in kcal. per mole)

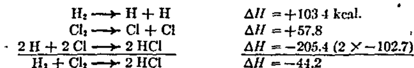
(Pauling, 1950)

BOND	BOND ENERGY	BOND	BOND ENERGY	BOND	BOND ENERGY
H—H	103.4	N—N	20.0	C=C	100
H—C	87.3	N—O	34.0 [a]	C=N	94
H—N	83.7	N—F	54	C=O	142 [b]
H—O	110.2	N—Cl	38.4	C=O	149 [c]
H—S	87.5	N—Br	33 [a]	C=O	152 [d]
H—F	133			C=S	103
H—Cl	102.7	O—O	34.9		
H—Br	87.3	O—S	72.1 [a]	N=N	46 [e]
H—I	71.4	O—F	44	N=O	68 [e]
		O—Cl	49.3		
		O—Br	49.8	O=O	118 [f]
C—C	58.6			O=S	120 [g]
C—N	48.6	S—S	63.8	S=S	101 [g]
C—O	70.0	S—Cl	66.1		
C—S	54.5			C≡C	123
C—F	92	F—F	33	C≡N	144 [h]
C—Cl	66.5	Cl—Cl	57.8	C≡N	150 [i]
C—Br	54.0	Br—Br	46.1		
C—I	45.5	I—I	36.2	N≡N	170 [j]

[a] Predicted.
[b] Formaldehyde.
[c] Other aldehydes.
[d] All other carbonyl groups including carbon monoxide.
[e] Rough approximation by the author.
[f] The oxygen molecule, O_2
[g] K. Pitzer, 1948
[h] Hydrogen cyanide
[i] Nitriles.
[j] The normal nitrogen molecule, N_2.

All reactions between gaseous atoms to form gaseous molecules evolve energy and are exothermic. When the above equations are written in the reverse order, the values of ΔH are all negative. Although here also such reactions can be written, usually their accomplishment is not practical, because gaseous atoms have very short lives. The hydrogen torch is, however, a practical example, for atomic hydrogen is formed as the stream of hydrogen gas passes through an electric arc, and recombination of hydrogen atoms helps to give the high temperature.

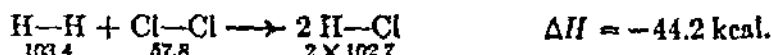
It is possible to calculate ΔH of reactions by a combination of simpler reactions, as for example, that of the gas phase reaction of hydrogen and chlorine to form hydrogen chloride. The reactions are written so that atomic hydrogen and atomic chlorine cancel out.



$$H_2 \longrightarrow H + H \qquad \Delta H = +103.4 \text{ kcal.}$$
$$Cl_2 \longrightarrow Cl + Cl \qquad \Delta H = +57.8$$
$$\underline{2\,H + 2\,Cl \longrightarrow 2\,HCl} \qquad \underline{\Delta H = -205.4\ (2 \times -102.7)}$$
$$H_2 + Cl_2 \longrightarrow 2\,HCl \qquad \Delta H = -44.2$$

It is evident that the reaction is exothermic, for $\Delta H = -44.2$ kcal. The product is more stable than the reactants. This is understandable if all of the hydrogen and chlorine is considered initially to be in the state of free uncombined atoms. When they combine to form H_2 and Cl_2, the heat evolved is 161.2 kcal. (103.4 + 57.8), but when they combine to form 2 HCl, the heat evolved is 205.4 kcal. Thus more energy is evolved when HCl is formed. This state represents a condition of lower energy, and thus of greater stability.

More simply, ΔH is obtained by subtracting the sum of the bond energies of the bonds formed, from the sum of the bond energies of the bonds broken. Thus, in the case of hydrogen chloride, it is convenient to write the bond energies below the respective bonds.



$$\underset{103.4}{\text{H—H}} + \underset{57.8}{\text{Cl—Cl}} \longrightarrow 2\,\underset{2\times 102.7}{\text{H—Cl}} \qquad \Delta H = -44.2 \text{ kcal.}$$

Whenever, by this procedure, the sum of the bond energies on the right is greater than that on the left, ΔH of the reaction towards the right is negative, and the reaction is exothermic. If, however, it should be less, then ΔH is positive and the reaction is endothermic. Any resonance energy should be treated as bond energy, and included as part of the energy of the bonds broken or formed, whichever the case may be. It is important to note that the number of bonds formed equals the number broken, and also that a double bond counts as two bonds and a triple bond as three bonds.

The values of ΔH obtained this way are reasonably accurate. However, the percentage error in the ΔH values may be quite large when ΔH is a small difference between large numbers, since bond energies are average values.

For liquid phase reactions ΔH may be obtained from bond energy values if heats of vaporization and of solution are known. Sometimes ΔH is satisfactory even if these additional data are disregarded, for often they are small relative to ΔH and in some cases they cancel, in case the heats of vaporization of reactants and products have essentially the same values. Sometimes in gaseous reactions the only liquid involved is water. This is true of many oxidations, especially of hydrocarbons. In order to calculate ΔH at 25° and one atmosphere, the heat of condensation of water vapor, *viz.*, 9.7 kcal. per mole, must be taken into account. Of course, heat is evolved during the process of condensation.

In this text many ΔH values of organic reactions are calculated from bond energies. The usefulness of a knowledge of energy changes in chemical reactions is pointed out in a subsequent section of this chapter.

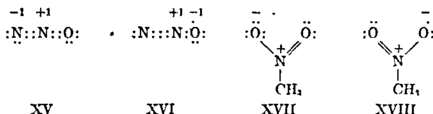
Bond energies are of value also in showing which of two or more possible arrangements of a given number of atoms in a molecule is the stable one, in case no decision can be reached on the basis of formal charges, as discussed later. The stable structure is the one for which bond energies are a maximum.

Resonance. Often, for a given arrangement of the atoms in the molecule of some particular compound, it is possible to write two or more arrangements of electrons. The structures so obtained are called electronic forms, some-

times electromers or electronic isomers. Usually they are called resonance forms of the molecule. In case two such forms are equivalent (as XVII and XVIII, below) they are not to be regarded as identical. They do have identical stabilities, however.

The actual structure is a combination of the different electronic forms, a sort of hybrid structure involving all of them. No one form can be said to represent the real structure of the molecule, nor can it be said that the molecule is in one form part of the time and in some other form or forms the rest of the time. Each form contributes to the overall structure. The contribution made by each form is in proportion to its relative stability. The molecule is said to resonate among the different electronic forms, and the phenomenon is known as resonance.

Resonance accounts for certain properties of molecules, and it is these properties which make it possible to detect resonance. The most important of these are enhanced stability and the alteration of bond distances and bond angles. These effects are apparent when the data on the structures of nitrous oxide and nitromethane are examined (Table 8, p. 20).



It is possible to write two electronic forms in which nitrogen is the middle atom, XV and XVI. In XV the two nitrogen atoms carry formal charges, one positive, the other negative, and in XVI one nitrogen carries a positive charge, and the oxygen a negative charge. These two forms would be expected to be more stable than XIV (p. 16). It is known from absorption spectra data that the middle atom is nitrogen (Table 8). Also the nitrogen-to-nitrogen distance is 1.10 Å, the same as the triple-bond distance, and the nitrogen-to-oxygen distance is 1.22 Å, close to the double-bond distance of 1.18 Å. It is concluded that there is resonance between the two forms, XV and XVI, and that, as a result of resonance, the bond distance is brought down close to the shorter distance. **Resonance produces bond shortening.** The bond angle in nitrous oxide is not altered by resonance, for it is the same in each resonance form, *viz.*, 180°, the same as in allene and methylacetylene, respectively (Table 6).

Resonance in nitromethane, XVII and XVIII, also produces bond shortening, for the nitrogen-to-oxygen distance is 1.21 Å, close to the double-bond distance, 1.18 Å, and much less than the single-bond distance, 1.36 Å (Table 8). Also bond angles are changed, for α and β become alike through resonance, and different from γ, whereas without resonance α and β would be different and α and γ would be alike.

Thus bond lengths and/or bond angles often do not conform to values calculated on the basis of a single electronic structure. Marked deviations from such values usually are best explained as the result of resonance involving two or more electronic forms

TABLE 8 | **Bond Distances and Bond Angles**

FORMULA	BOND	BOND DISTANCE		BOND ANGLE			
		calc.	obs.	identified	calculated	observed	predicted (with resonance)
N≡N—O (angle α at N)	N≡N	1.10 Å	1.10 Å	α	180°	180°	
	N—O	1.36	1.22				
N=N=O (angle α at N)	N=N	1.22	1.10	α	180°	180°	
	N=O	1.18	1.22				
CH_3—N(=O)—O (angles α, β, γ)	N=O	1.18	1.21	α	125° 16′	116°	117°
	N—O	1.36	1.21	β	109° 28′	116°	117°
	C—N	1.47	1.47	γ	125° 16′	128°	126°

Effect of Resonance on Bond Energies. Resonance increases the stability of a molecular system by stabilization of the bonds. The extent to which the molecule is stabilized, when calculated from bond energies, is called the resonance energy of the molecule. In the case of many organic molecules it can be calculated from heats of formation and/or heats of combustion. When the heat of formation from the elements of an organic compound is greater than calculated, or the heat of combustion is lower than calculated, the molecule is stabilized by resonance. The difference between observed and calculated values is the resonance energy. In Table 9 are listed the resonance energies of many types of organic compounds.

Molecular Stability. Comparing diatomic molecules of similar type, the higher the bond energy the more stable the molecule. This results from the fact that a greater amount of energy must be absorbed before the bond can be broken. Thus the stability of hydrogen halides increases in the order HI, HBr, HCl, HF, because the respective bond energies are 71.4, 87.3, 102.7, and 147.5 kcal. per mole.

In a triatomic or more complex molecule the sum of bond energies and resonance energies is a measure of the stability. If there are two or more isomers, that is, two or more compounds which have the same atoms in the molecules but differently arranged, the most stable form can be selected on

the basis of bond and resonance energies, and is the one for which the sum of these is a maximum. Oftentimes a less stable form changes to a more stable form so very slowly that both can exist. In such cases the difference in sta-

TABLE 9 | Some Empirical Resonance Energy Values

(Pauling, 1939)

COMPOUND	GROUP	RESONANCE ENERGY
Carbon monoxide	C=O	58
Carbon dioxide	O=C=O	33
Carbonate ion	$CO_3^{=}$	42
Carbon oxysulfide	O=C=S	20
Carbon disulfide	S=C=S	11
Nitric acid	HO—NO_2	25
Nitrate ion	NO_3^-	45
Alkyl cyanates	R—N=C=O	7
Aliphatic acids	R—(C=O)—OH	28
Esters	R—(C=O)—OR′	24
Carboxylate ions	R—(C=O)—O^-	36
Dialkyl carbonates	RO—(C=O)—OR	42
Amides	R—(C=O)—NH_2	21
Urea	H_2N—(C=O)—NH_2	37
Guanidine	H_2N—(C=NH)—NH_2	47
Butadiene	C_4H_6	3
Benzene	C_6H_6	39
Naphthalene	$C_{10}H_8$	75
Anthracene	$C_{14}H_{10}$	105
Phenanthrene	$C_{14}H_{10}$	110
Pyridine	C_5H_5N	43
Quinoline	C_9H_7N	69
Pyrrole	C_4H_5N	31
Indole	C_8H_7N	54
Furane	C_4H_4O	23
Thiophene	C_4H_4S	31
Biphenyl	C_6H_5—C_6H_5	8 [a]
Phenylethylene	C_6H_5—CH=CH_2	7 [a]
Stilbene	C_6H_5—CH=CH—C_6H_5	15 [a]
Phenylacetylene	C_6H_5—C≡CH	10 [a]
Phenol	C_6H_5—OH	7 [a]
Aniline	C_6H_5—NH_2	6 [a]
Benzaldehyde	C_6H_5—(C=O)—H	4 [a]
Acetophenone	C_6H_5—(C=O)—CH_3	7 [a]
Benzophenone	C_6H_5—(C=O)—C_6H_5	10 [a]
Benzoic acid	C_6H_5—(C=O)—OH	4 [a, b]
Phenyl cyanide	C_6H_5—C≡N	5 [a]

[a] Additional to the 39 of benzene.
[b] Additional to the 28 of acids.

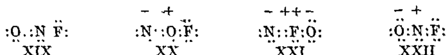
bility usually is small. Sometimes one form is so unstable that it cannot be isolated. This is often the case when there is a large difference in stability.

Often it is possible to make predictions in regard to the relative stabilities of isomeric forms on the basis of formal charges. Such predictions are es-

pecially useful when bond energies are not known or are not available, for they can be made easily and rapidly.

Formal Charges and Relative Stabilities. An isomer having formal charges in general is less stable than an isomer without any charges, and the effect is as follows: (1) minor, if the more electronegative element carries the negative charge; (2) significant, if the atoms which carry the positive and negative charges have the same electronegativities; (3) great, if the more electropositive element carries the negative charge; (4) very great, when adjacent atoms carry charges of the same sign (the adjacent charge rule). The electronegativities of the elements are shown in Figure 5, The Electronegativity Map, page 34.

Selection of the most stable isomer by means of formal charges is especially well exemplified in the case of nitrosyl fluoride. The selection here cannot be made by means of bond energies, for the values of some of the bond types are not known, but it can be made on the basis of formal charges. There are three possible arrangements for the molecule, which is known to be linear, depending on which atom is the middle one. In order to have a similar basis of comparison, it is desirable that the isomeric forms be alike in having complete octets and the same number of shared electrons (XIX, XX, and XXI).



In XIX there are no formal charges, in XX oxygen, the more electronegative element, carries a positive charge, and in XXI, fluorine, the most electronegative element, carries a doubly positive charge. The difference in stability is so great that XX and XXI do not exist. The structure of nitrosyl fluoride is XIX. Other resonance forms can be written, but it will be observed that if these are written with complete octets, they are less stable than the corresponding electronic forms above. Other forms can be written with an atom having an incomplete octet, and these can be more stable.

Excited Forms. These are electronic forms which have low stabilities relative to the stable or **unexcited** form. They have a higher energy content. The extra energy can cause a greater contribution of less stable forms to the overall structure. Thus, in the case of nitrosyl fluoride, the contribution of XXII is increased as energy is absorbed. The nitrogen atom in XXII does not possess a complete octet of electrons Absorption of still more energy may lead to bond rupture, with dissociation into two gaseous particles.

Chemical reactivity depends upon activation. On this account some attention will be devoted in this text to the way catalysts act to promote reactions of organic compounds.

Energy Change and Equilibrium. Reactions generally take place in the direction in which energy is evolved. Exothermic reactions are much more common than endothermic reactions. Moreover, a reaction in which

disappear, so that for practical purposes there is no reversal. On the other hand, many reactions in which the energy change is slight do not proceed to completion, but come to equilibrium, since the reverse reaction becomes prominent as the amounts of products increase. If two substances, A and B, react to form two other substances, C and D, and these in turn react to form A and B (eq. 1)

$$A + B \rightleftharpoons C + D \tag{1}$$

the equilibrium constant, K, is a measure of the extent to which reaction takes place (eq. 2)



$$K = \frac{[C][D]}{[A][B]} \tag{2}$$

Here [A], [B], [C], and [D] represent the respective concentrations of reactants and products at equilibrium. Thus if essentially all of A and/or B disappears, K will have a very large value, while if only about half of A and B react, K will be close to unity.

The equilibrium constant K of a reaction is related to the change in energy of the system, ΔH, by equations 3 and 4.

$$RT \ln K = -\Delta F \tag{3}$$

$$\Delta H = \Delta F + T\Delta S \tag{4}$$

Here R is the gas constant, 1.99 calories per mole, T is the temperature on the absolute scale, ln K is the natural logarithm of the equilibrium constant, and ΔF is the sum of the free energies of the reactants minus the sum of the free energies of the products, expressed in calories. The standard free energy *of a compound*, ΔF°_{298}, *is defined as the change in the free energy of a* system when a compound is formed from the elements at 25° C (298° K) and one atmosphere. The standard free energies of elements are taken as zero. The change in free energy during a reaction, ΔF, is the energy which is available for doing work. $T\Delta S$ is related to the change in the entropy of the system. This form of energy is not available for doing work. Thus the equilibrium constant is related indirectly to ΔH. Equation 3 becomes equation 5 at 298° K (25° C) when ΔF is expressed in kilocalories.

$$\log_{10} K = -\Delta F/1.363 \tag{5}$$

The energy changes involved in the formation of the hydrogen halides from the elements in their standard states have been accurately determined, ΔH experimentally by direct measurement and $T\Delta S$, the entropy change term, from heat capacity measurements on the three substances involved in each of the four reactions. Thus the values of ΔF and K can be calculated. In the case of hydrogen iodide, the equilibrium constant can be obtained comparatively easily by direct measurement. In Table 10 are listed the thermodynamic data for the combination of hydrogen with the halogens at 25° one atmosphere pressure.

The data of Table 10 show that the reaction of hydrogen with fluorine is the most strongly exothermic of the four reactions, since $-\Delta H$ has the greatest value, and that the reaction with iodine is the least exothermic. Actually the last reaction is endothermic, since ΔH is positive. The equilibrium constant *is largest in the most strongly exothermic reaction, and smallest in the* least, that is, the reactants are more completely used up when the most energy is evolved.

In general, the values of ΔF are not far from those of ΔH, except in the case of hydrogen iodide. The entropy change in the formation of hydrogen chloride is quite small, since the number of molecules of products is the same as the number of molecules of reactants, and products and reactants are alike as regards complexity and physical state. Whenever these conditions hold, $T\Delta S$ usually is quite small, of the order of 1 to 3 kilocalories. When products and reactants are dissimilar in regard to number, complexity, or physical state, the $T\Delta S$ term may become significant, but even then it does not often *exceed* ± 15 *kcal. and usually is numerically less than* ± 10 *kcal. in reactions* where one or two molecules are reacting to form one or two other molecules. The discrepancies between ΔF and ΔH in Table 10 are due to dissimilarities in molecular complexity or in physical state between reactants and products. Thus hydrogen fluoride is polymerized, bromine is a liquid, and iodine is a solid.

TABLE 10 — *Thermodynamic Data in the Formation of the Hydrogen Halides*

COMPOUND	$\Delta H°$ OF FORMATION kcal./mole	$T\Delta S°$ OF FORMATION kcal./mole	$\Delta F°$ OF FORMATION kcal./mole	EQUIL. CONST. K
HF	−64.5	−2.7	−61.8	5.6×10^{47}
HCl	−22.0	+0.7	−22.7	4.2×10^{16}
HBr	−8.6	+4.3	−12.9	2.9×10^{9}
HI	+6.4	+8.4	−2.0	2.9×10

It is desirable to ascertain ΔF for a given reaction, for then it is possible to calculate an equilibrium *constant for the reaction. Tables of the free energies* of formation of compounds from the elements are available, and many values for organic compounds are known. Unfortunately these constitute only a small percentage of the known organic compounds. However, ΔH of *numerous gaseous reactions can be approximated from bond energies.* When the $T\Delta S$ value is small relative to ΔH, the latter may be regarded as approximating ΔF, and used for calculating an approximate equilibrium constant. In order to obtain ΔH when a reaction takes place in the liquid phase, heats of vaporization *and of solution must be considered.* In the case of quite a few organic reactions, ΔH can be calculated quite accurately from heats of combustion (see Table 22, p. 57).

PROBLEMS

1. Determine the number of electrons shared between octets, and write a possible structure for:

a) $HOCl$	*e*) $CaSO_4$	*i*) $(NH_4)_2S$
b) K_2SO_3	*f*) $Ba(NO_3)_2$	*j*) $H_2S_2O_4$
c) $NaNO_2$	*g*) SCl_2	*k*) $K_2S_2O_4$
d) $KBrO_3$	*h*) $SOCl_2$	*l*) Na_2HPO_4

2. For the following write the stable structure and two other isomeric structures, but not more than two, all with complete octets. Show how it is possible to select the stable structure from a consideration of formal charges and/or resonance. Write cyclic formulas only when necessary.

a) $NOBr$	*f*) N_2O_3	*k*) HNO_2	*p*) CF_3Cl	*u*) $C_2H_4O_2$
b) CO_2	*g*) HPO_3	*l*) NH_4I	*q*) $COBr_2$	*v*) CH_4O_3S
c) CS_2	*h*) K_2SO_3	*m*) CF_4	*r*) KNO_3	*w*) CH_3ON
d) COS	*i*) $KHCO_3$	*n*) $COCl_2$	*s*) SO_2Cl_2	*x*) $C_2H_6S_2$
e) NF_3	*j*) PCl_3	*o*) NO_2F	*t*) $KHSO_4$	*y*) $SOCl_2$

3. From bond energy and resonance values, calculate ΔH for the following gaseous reactions:

a) $Br_2 + H_2 \longrightarrow 2\,HBr$
b) $I_2 + H_2 \longrightarrow 2\,HI$
c) $2\,CO + O_2 \longrightarrow 2\,CO_2$
d) $3\,F_2 + N_2 \longrightarrow 2\,NF_3$
e) $3\,Cl_2 + N_2 \longrightarrow 2\,NCl_3$
f) $C_2H_2 + H_2 \longrightarrow C_2H_4$
g) $2\,Cl_2 + O_2 \longrightarrow 2\,Cl_2O$
h) $CO + Cl_2 \longrightarrow COCl_2$
i) $2\,F_2 + O_2 \longrightarrow 2\,F_2O$
j) $2\,H_2 + N_2 \longrightarrow N_2H_4$
k) $2\,COCl_2 + O_2 \longrightarrow Cl_2 + 2\,CO_2$
l) $CO_2 + 4\,HF \longrightarrow CF_4 + 2\,H_2O$

4. Calculate ΔH for the following reaction at 25° and one atmosphere, using: (*a*) bond energies and any other data but neglecting heats of solution; (*b*) ΔH of formation from the elements (see handbooks or *International Critical Tables;* state source).

a) $CH_4 + 2\,O_2 \longrightarrow 2\,H_2O + CO_2$
b) $CO + 3\,H_2 \longrightarrow H_2O + CH_4$
c) $C_2H_2 + 2.5\,O_2 \longrightarrow H_2O + 2\,CO_2$
d) $NH_4O + H_2O \longrightarrow H_2O + NH_3$
e) $Cl_2O + 2\,H_2 \longrightarrow H_2O + 2\,HCl$

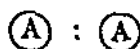
5. The carbon-to-fluorine bond distance in CH_3F is 1.42 Ångstrom units, in CH_2F_2, 1.36 Ångstrom units, and in CF_4, 1.36 Ångstrom units. How do you account for these differences?

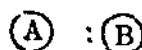
CHAPTER 3 Electric Dipole Moments and Electronegativities

It was pointed out in Chapter 2 that there are two extreme types of chemical bonds, *viz.*, the ionic and the covalent. The most common ionic type results from the complete transfer of an electron from the valence shell of one atom, that of a strongly metallic element, to the valence shell of another atom, that of a nonmetallic element. Typical examples are found in such compounds as sodium chloride, potassium sulfate, calcium oxide, etc. The ionic type may result also from the transfer of a proton from any atom to any other atom, as in ammonium chloride. The pure covalent type of chemical bond is an electron pair between like atoms, or atoms of similar electronegativity, as for example the bonds in H—H and Cl—Cl.

There is a modified covalent bond which is intermediate between the ionic type and pure covalent type. This is a shared-electron bond between atoms of unlike electronegativities, as the bonds in CO_2, NH_3, and HCl. A bond of this character, although of the covalent type, differs from a pure covalent bond in possessing some of the characteristics of the ionic type of bond. The ionic bond, the pure covalent bond, and the covalent bond between different atoms are shown by I, II, and III, respectively, where ⊕ and ⊖ represent positive and negative ions, and Ⓐ and Ⓑ represent atoms of elements *A* and *B*.


I


II


III

Here *B* is more electronegative than *A* and thus exerts a stronger attraction for the shared-electron pair.

In I, the two ions, oppositely charged, are held together by powerful coulomb attraction. This picture is an oversimplification, for other ions are in the vicinity. In solid sodium chloride, for example, each positive sodium is equidistant from six negative chlorine ions and *vice versa*.

In II the shared electrons are represented as being equidistant from the two atoms, to indicate that they are attracted equally by them. This is a pure covalent bond. In III the shared electrons are shown closer to atom *B*,

to indicate that atom B exerts the greater attraction for these electrons. This is still a covalent bond but it possesses some ionic character.

Electric Dipole Moments. Substances are called ionic, polar, and nonpolar according to whether their molecules possess large, intermediate, or zero electric dipole moments. A substance has zero dipole moment when the center of positive charges coincides with the center of negative charges, and a finite moment when there is a separation between these centers Ionic compounds have the highest dipole moments, because they are composed of positively and negatively charged ions that cannot occupy the same space. The way these unit particles differ is indicated by IV, V, and VI, where IV represents two discreet particles (the ions) and V and VI represent molecules.



In IV and V the centers of positive and negative electricity do not coincide and in VI they do. The nonuniformity of the electric field about V can be shown by partial charges, $\delta+$ and $\delta-$, as in VII.

The dipole moment, which measures the extent to which there is a separation of charges in the molecule (for ionic compounds the measurement must be made in the vapor state), is expressed by equation 6.

$$\mu = ed \tag{6}$$

Here μ is the dipole moment, e is the electronic charge, and d is the distance in centimeters between the centers of positive and negative charges. For unit electrical charge separated one Ångstrom unit, μ has the value shown by equation 7,

$$\mu = 4.8 \times 10^{-18} \text{ esu} = 4.8\ D \tag{7}$$

because the charge on the electron is 4.77×10^{-10} electrostatic units and one Å is 10^{-8} centimeters. The unit of dipole moment is 10^{-18} esu, called the Debye (D).

Electric dipole moments of some substances are shown in Table 11. All monatomic molecules have zero moment. Of diatomic molecules, symmetrical ones, such as H—H, Cl—Cl and N≡N have zero moment by cancellation and unsymmetrical ones, such as H—Cl and H—Br, have finite moments A zero moment in more complicated molecules means that individual bond moments cancel. Usually cancellation is due to a symmetrical arrangement.

The high dipole moment of the potassium iodide molecule is due to its ionic structure. The molecular form is observed only in the gaseous state, at a high temperature. The separation of charges, that is, the distance between atomic centers, can be calculated from the dipole moment, and is found to be 2.1 Å.

TABLE 11 | Electric Dipole Moments of Some Gas Molecules (in Debye units)

He	0	C_6H_6	0	PCl_3	1.16 [a]	H_2O	1.84
Ne	0	C_6H_{14}	0	$SOCl_2$	1.38 [a]	CH_3Cl	1.86
H_2	0	SiH_4	0	NH_3	1.46	H_2O_2	2.1 [a]
N_2	0	N_2O	0.2	CH_2Cl_2	1.6	HCN	2.1
O_2	0	HI	0.38	SO_2	1.60	CH_3COCH_3	2.8
Cl_2	0	PH_3	0.55	CH_3I	1.62	$HCONH_2$	3.21 [b]
BF_3	0	HBr	0.78	SO_2Cl_2	1.64	CH_3NO_2	3.8
CH_4	0	H_2S	0.93	CH_3OH	1.68	CH_3CN	3.9
CCl_4	0	$CHCl_3$	1.0	CH_3Br	1.79	$SbCl_3$	4.0 [a]
CO_2	0	HCl	1.03	Cl_2O	1.7	KI	10 [c]

[a] From measurements in dilute solution
[b] At 152°.
[c] At 630°.

Dielectric Constants. These are important constants because first, dipole moments are calculated from them, and second, many important properties of substances are related to them. The dielectric constant is obtained from measurement with an electric condenser. When the condenser contains some medium, gaseous or liquid, the capacity of the condenser is increased over its capacity in a vacuum. The ratio of the capacity when the dielectric is present to the capacity in a vacuum is the dielectric constant. The constant is measured also by noting the field strength at some particular place with and without a dielectric present. Here again it is the ratio between the respective values.

There are two factors contributing to the dielectric properties of a medium, namely, the permanent dipole moment μ and the induced dipole moment μ_{ind}. The permanent dipole results from the fact that the centers of positive and negative charges do not coincide, as already described. The induced moment arises from the effect of the electric field on the electrons and nuclei of the molecules, the electrons being displaced within the molecule towards the positively charged plate of the condenser, the nuclei towards the negative plate. The extent to which this shifting takes place is related to the polarizability, α. Actually the resulting polarization is largely due to electron shifting. The polarizability of molecules is considered to be quite important in chemical reactivity because of the effect that the electrical field of the molecules of one substance may have on the electrical distribution of another.

In Figure 4 are shown the random orientation of molecules before the plates of the condensers are charged and the orientation of the molecules after the plates are charged. The arrows represent the permanent dipole moments in the molecules. The molecules become oriented so that the negative ends of the permanent dipoles point towards the positive plate. The plus and minus signs represent the charges induced in the molecules by the displacement of electrons and nuclei by the field. These charges represent the induced mo-

ment, which results from the increase in separation distance between the centers of positive and negative charges. The induced moment is greater, the greater the value of α, the polarizability. Because of these two effects, *viz.*, the molecular orientation and the polarization, the dielectric medium acts as a depolarizer. This allows a greater charge to be built up in the condenser.

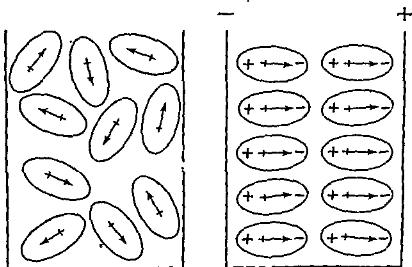


Figure 4 · Random Orientation of Polar Molecules (left), and Orientation in an Electric Field

The relationship of the dielectric constant, ϵ, to dipole moment μ and polarizability, α, is given by equation 8.

$$P = \frac{\epsilon - 1}{\epsilon + 2}\frac{M}{\rho} = \frac{4\,\pi N}{3}\left(\frac{\mu^2}{3\,kT} + \alpha\right) \tag{8}$$

Here P is the molar polarization, M, molecular weight, ρ, density, N, Avogadro's number, k, the Boltzman constant, and T, the absolute temperature. The right-hand term of equation 8 is derived from equation 9,

$$P = P_\mu + P_\alpha \tag{9}$$

where P_μ is the molar polarization due to the permanent dipole moment and P_α is that due to the polarizability. Experimentally, P_μ and P_α can be evaluated by measuring P in both a low-frequency and a high-frequency field. At the low frequency $P = P_\mu - P_\alpha$, but at the high frequency $P = P_\alpha$. Under these conditions P_μ is zero, because the molecules do not have sufficient time to become oriented. A similar relationship holds at high temperatures, where the greater rotational energy of the molecules tends to counteract the orienting power of the field. Thus P_α is the part of P that is independent of frequency and temperature.

It is seen from equation 8 that if the dielectric constant were unity the term that includes both the dipole moment and polarizability (that is, the term in parentheses) would be zero; thus both μ and α would be zero if they

have the same sign. This same term increases as the dielectric constant increases. Values of dielectric constants of some liquids are shown in Table 12. It is noted that the liquids of low dielectric constant are those of low dipole moment, Table 11.

TABLE 12 | **Dielectric Constants of Some Liquids**

Hexane	1.9	Arsenic trichloride	12.3
Arsine	2.0	Phosphorus oxychloride	14
Carbon tetrachloride	2.2	Ammonia	15
Carbon bisulfide	2.6	Acetone	21
Hydrogen iodide	2.9	Ethanol	24
Bromine	3.2	Antimony trichloride	33 [a]
Hydrogen bromide	3.8	Methanol	33
Ethyl ether	4.3	Methyl cyanide	37
Hydrogen chloride	4.6	Nitromethane	39
Chloroform	5.0	Hydrogen fluoride	65 [b]
Hydrogen sulfide	5.6	Water	80
Thionyl chloride	9.0	Formamide	84
Sulfuryl chloride	9.1	Sulfuric acid	>84
Ethyl bromide	9.4	Hydrogen peroxide	87 [c]
Methyl amine	10	Hydrogen cyanide	118
Sulfur dioxide	12		

[a] At 75°. At 20° the value probably would be about 20.
[b] By extrapolation from measurements at 0°
[c] By extrapolation from measurements on 46 per cent aqueous solution.

Properties as Related to Polar Characteristics. Physical properties are closely related to the dipole moment and the dielectric constant. In Table 13 are listed a number of substances, showing how the boiling point and melting point, which in general rise with increase in molecular weight, are raised more when there is a finite dipole moment. This is due to the greater attraction between molecules when they possess a dipole moment. If hydrogen bonding can take place, the attraction between molecules is so intensified that the average molecular weight is measurably greater than that corresponding to the formula; for example, water sometimes is considered to be $(H_2O)_2$. The formation of associated molecules has a pronounced effect on the dipole moment, owing to the increased separation of charge. Salts have very high melting points, owing to the large amount of energy that must be absorbed to overcome the large attraction between oppositely charged ions.

Ionic substances in the fused state are excellent conductors, for then the ions, of which the compound is composed, are free to move past each other. Polar and nonpolar liquids have low conductivities, owing to absence or essentially complete absence of ionization.

Solvents having high dielectric constants are able to dissolve many typical salts like the alkali halides. This is because such a solvent decreases the attraction between oppositely charged ions, owing to its depolarizing action.

Solvents of low dielectric constant do not dissolve ionic compounds such as sodium chloride and similar substances.

TABLE 13 | **Relation of Freezing Point and Boiling Point of Liquids to Formula Weight and Dipole Moment**

SUBSTANCE	FORMULA	FORMULA WEIGHT	SUBSTANCE OF ZERO DIPOLE MOMENT			SUBSTANCE OF FINITE DIPOLE MOMENT		
			μ	f.p.	b.p.	μ	f.p.	b.p.
Hydrogen	H_2	2	0	−259 1	−252.7			
Helium	He	4	0	−272.2	−268 9			
Methane	CH_4	16	0	−182.6	−161.4			
Ammonia	NH_3	17				1.46	−177.7	−33 4
Water	H_2O	18				1.84	0	100
Neon	Ne	20	0	−248 7	−245.9			
Hydrogen cyanide	HCN	27				2 1	−12	25
Nitrogen	N_2	28	0	−209 9	−195 8			
Methylamine	CH_3NH_2	31				1.0	−92	−6.7
Oxygen	O_2	32	0	−218 4	−183 0			
Silane	SiH_4	32	0	−185	−112			
Methyl alcohol	CH_3OH	32				1.68	−98	64.7
Hydrogen sulfide	H_2S	34				0.93	−82.9	−59 6
Hydrogen chloride	HCl	37				1 03	−111	−85
Argon	A	39	0	−189	−185			
Methyl cyanide	CH_3CN	41				3 9	−41	82
Carbon dioxide	CO_2	44	0	−56	−78			
Nitrous oxide	N_2O	44	0 1	−102	−90			
Formamide	$HCONH_2$	45				3.2	2	193
Methyl chloride	CH_3Cl	50				1.86	−97	−24
Nitromethane	CH_3NO_2	61				3 8	−28	101
Sulfur dioxide	SO_2	64				1.6	−75	−10
Boron fluoride	BF_3	68	0	−127	−101			
Chlorine	Cl_2	71	0	−108	−34			
Propionic acid	C_2H_5COOH	74				1 6	−22	141
Krypton	Kr	83	0	−169	−152			
Hexane-*n*	C_6H_{14}	86	0	−94	69			
Methyl bromide	CH_3Br	95				1.79	−93	4 5
Thionyl chloride	$SOCl_2$	118				1.38	−104	79
Chloroform	$CHCl_3$	119				1.86	−63	61
Xenon	Xe	131	0	−140	−109			
Sulfuryl chloride	SO_2Cl_2	135				1 64	−54	69
Methyl iodide	CH_3I	142				1.62	−64	42
Carbon tetrachloride	CCl_4	154	0	−22	76			
Bromine	Br_2	160	0	−7.2	59			

There are some general relationships between the polar nature of substances and their properties. These are summarized in Table 14. At the two extremes are the ionic and nonpolar types; polar substances are seen to be intermediate.

Bond Dipole Moments. These are calculated from molecular dipole moments. In a diatomic molecule, for example a hydrogen halide, the molecular

moment is considered to be the bond dipole moment, because the shift of the shared electron pair towards the halogen atom is the cause of the separation of the centers of positive and negative charges. (This is an oversimplifica-

TABLE 14 | Properties of Substances in Relation to their Polar Characteristics

PROPERTY	IONIC	POLAR	NONPOLAR
Dipole moment	high	intermediate	zero
Dielectric constant	high	intermediate	low
Melting point	high	intermediate	low
Boiling point	high	intermediate	low
Conductivity, as liquid or fused	high	low	very low
Ionization, as solute	high	low	very low
Ionizing power, as solvent	high	high to low	very low
Molecular structure	none	fixed	fixed
Association	ionic packing	high to low	very low
Reactivity	high	variable	low

tion, for there can be some modification of other electron orbits.) In more complicated molecules the molecular moment is the vector sum of the various bond dipole moments. From a knowledge of bond angles and bond distances in individual molecules, and the dipole moments of numerous molecules, bond dipole moments have been established for a large number of bonds. The most important ones, from the standpoint of organic chemistry, are listed in Table 15. Here the conventional arrow with crossed shaft points towards the more electronegative element, and indicates that the electrons of the bond are shifted in that direction.

Ionic Character in Covalent Bonds. The dipole moment of 1.03 *D* in the hydrogen chloride molecule is due to the shift of the shared-electron pair towards the chlorine atom, and that of 10 *D* in the gaseous potassium iodide molecule is due to the complete transfer of an electron from potassium to iodine. It is possible to calculate the per cent of ionic character in the hydrogen chloride bond if three assumptions are made: (1) The H—Cl bond distance remains constant at 1.28 Å; (2) a purely covalent H—Cl bond would have zero dipole moment, for there would be no electron shift, and the bond would be like the ones in H—H, Cl—Cl, etc.; (3) a purely ionic H^+Cl^- bond would have a dipole moment of 6.14 *D*, because in that case there would be a complete transfer of an electron from hydrogen to chlorine; the value of μ would be $(1.28 \times 10^{-8})(4.8 \times 10^{-10})$ (p. 27). Thus the per cent of ionic character is considered to be the ratio of 1.03 *D*, the observed dipole moment, to 6.14 *D*, the moment calculated for 100 per cent ionic character. This is 17 per cent. Thus, although the bond in gaseous HCl is a covalent (shared-electron) bond, it possesses some of the characteristics of an ionic bond, re-

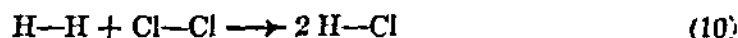
sulting from the electron shift. It is, in essence, a polarized bond; similarly, for the H—Br bond, 11 per cent, and for the H—I bond, 5 per cent ionic character.

TABLE 15 | **Bond Dipole Moments**

BOND ↛	DIPOLE MOMENT *D*	SEPARATION DISTANCE Å	BOND ↛	DIPOLE MOMENT *D*	SEPARATION DISTANCE Å
H—I	0.38	1.63	C—I	1.2	2.10
H—Br	0.78	1.34	C—Br	1.4	1.91
H—Cl	1.03	1.28	C—Cl	1.5	1.76
H—O	1.51	0.96	C—F	1.4	1 41
H—N	1.31	1.00	C—O	0.8	1 43
H—S	0.68	1.37	C—N	0 4	1.47
H—C	0.4	1.07	C—S	1.0	1.81
N—O	0 5	1.36	N=O	1.9	1.16
C=C	0	1.34	C≡C	0	1.20
C=O	2.5	1.24	C=S	3 0	1.62
			C≡N	3 3	1.15

Multiple bonds between unlike elements have much higher dipole moments than the corresponding single bonds, even though the interatomic distance is less. This is important in connection with the reactions of many organic compounds.

A covalent bond having some ionic character is more stable than the mean of the two pure covalent bonds from which it is formed. In the reaction of equation 10 the two H—Cl bonds are more stable than the mean of H—H and Cl—Cl by 44.2 kcal. per mole, or 22.1 kcal. per H—Cl bond.



$$\text{H—H} + \text{Cl—Cl} \longrightarrow 2\,\text{H—Cl} \qquad (10)$$

The extra stability is explained by Pauling as the result of resonance between the covalent bond and the ionic bond.

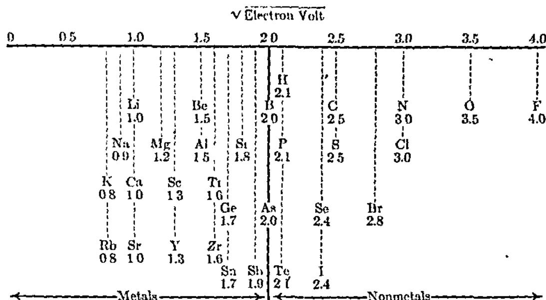


$$\text{H—Cl} \longleftrightarrow \text{H}^+ + \text{Cl}^-$$

Even in a pure covalent bond there is some ionic character. For example, it has been calculated that there is some contribution, about 5 per cent, of H^+ and H^- to the H—H covalent bond. In the H—Cl bond the ionic character is greater, namely 17 per cent. As in other cases where resonance is present, an extra stability exists. In general, the greater the amount of ionic character in a shared-electron bond the greater the stability of the bond.

The Electronegativity Map. On the assumption that the extra stability of heterovalent bonds is due to the combination of covalent and ionic character, a quantitative scale of electronegativities has been constructed by Pauling (see Electronegativity Map, Fig. 5) such that, with its means, it is possible to calculate for any bond the extra stability resulting from its ionic

character. This extra stability, which is designated as Δ in this connection, actually is Δ*H* of the reaction when the respective elements react to form the bond.



One international electron volt = 23.07 kcal. per mole.

Pauling, Nature of the Chemical Bond, Cornell University Press, 1940, p. 65

Figure 5 • The Electronegativity Map, Showing Relative Electronegativities of the Elements

In the electronegativity map the scale is in $\sqrt{\text{e.v.}}$ (One electron volt is 23.07 kcal. per mole.) The value of 2.0 is taken to represent the middle of the scale; elements to the left of this are the metallic elements, those to the right, the nonmetallic. The way in which this scale can be used is illustrated in the case of hydrogen chloride. Indicating electronegativities by the symbols x_A and x_B, the extra stabilization energy Δ in the bond H—Cl, in comparison to the mean of H—H and Cl—Cl, is given by equation 11

$$\Delta = 23.07(x_A - x_B)^2 \tag{11}$$

In the case of hydrogen chloride, where the electronegativities are 2.1 and 3.0 respectively, $(x_A - x_B)^2 = 0.81$, and Δ is 19.0 kcal. This compares with the actual value of 22.0 kcal. (Table 10, p. 24). This is a reasonable check, since 0.1 e.v. corresponds to about 2 kcal.

The electronegativity map is of value because it furnishes not only a basis for calculating approximate heat changes in reactions between elements, but also a scale for comparing the electronegativities of the elements quantitatively. It is evident that fluorine, at 4.0, is the most electronegative element, oxygen at 3.5 is second, and chlorine and nitrogen at 3.0 are next. Also, the alkali metals are the most electropositive elements. It is seen, therefore, that the electronegativity map demonstrates in a quantitative way the fundamental principle that when elements react, the heat evolved is greater, the greater the difference in electronegativities.

Hydrogen, electronegativity 2.1, is essentially neutral and carbon at 2.5 is somewhat electronegative. The signs of the bond dipole moments in Table 15 are seen to be in agreement with electronegativities. In general, ionic character calculated from bond dipole moments agrees fairly well with that calculated from electronegativities, but there are a number of cases where the agreement is not very good.

Electronegativities of Radicals. In organic chemistry the nature of the atom or radical attached to a carbon atom profoundly affects chemical reactions of organic compounds. The effect that a radical can exert may be of considerable importance from the standpoint of the nature of such reactions, the rate with which they take place, and the equilibria involved. An important part of this influence is due to the electronegativity of the radical, *i.e.*, the effect which it exerts upon the electrons of the bond joining it to the carbon atom. The electronegativity depends mainly upon the nature of the element or elements which comprise the radical and to a less extent upon the element to which the radical is attached. The order of electronegativity of radicals varies somewhat in different types of compounds. For organic chemistry, the electronegativity of radicals joined to carbon is important.

An approximate order of relative electronegativities of radicals is obtained from the values of the dipole moments of organic compounds in which these radicals are attached to a similar organic radical. A better relationship would be given by the dipole moments of the bonds concerned, but many of these are not available. In Table 16 are listed a number of radicals, Y, the

TABLE 16 **Electric Dipole Moments of Alkyl Compounds and Ionization of Hydroxy Compounds**

RADICAL Y		μ OF R ↔ Y[a]	HYDROXY COMPOUND, Y—OH		
name	formula	D	name	formula	K_a
Nitro	—NO_2	−3.8	Nitric acid	HO—NO_2	large
Nitroso	—NO	−2.5	Nitrous acid	HO—NO	4×10^{-4}
Formyl	—CHO	−2.5	Formic acid	HO—CHO	1.8×10^{-4}
Cyano	—CN	−3.9	Cyanic acid	HO—CN	1.2×10^{-4}
Benzoyl	—COC_6H_5	−3.0	Benzoic acid	HO—COC_6H_5	6.3×10^{-5}
Acetyl	—$COCH_3$	−2.8	Acetic acid	HO—$COCH_3$	1.8×10^{-5}
Chloro	—Cl	−1.8	Hypochlorous acid	HO—Cl	6.7×10^{-10}
Phenyl	—C_6H_5	−0.4	Phenol	HO—C_6H_5	1.3×10^{-10}
Hydroxyl	—OH	−1.7	Hydrogen peroxide	HO—OH	2.4×10^{-12}
Hydrogen	—H	0	Water	HO—H	2×10^{-16}
Methyl	—CH_3	0	Methanol	HO—CH_3	1×10^{-17}
Ethyl	—C_2H_5	0	Ethanol	HO—C_2H_5	7.3×10^{-20}

[a] R is $(CH_3)_2CH$ or $(CH_3)_3C$—.

dipole moment of compounds, R—Y, in which these radicals are joined to an aliphatic carbon atom, and the acidic ionization constants of hydroxy compounds, Y—OH. The component of the dipole moment of R—Y, in the

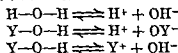
direction of the bond R—Y, has its negative end towards Y. The acidity of Y—OH is roughly proportional to the dipole moment of R—Y.

In general, the acidic ionization of Y—OH is greater the larger the dipole moment of the organic compound. The nitro group is the most electronegative radical in the table.

The mechanism by which radicals promote ionization of Y—O—H may be one or all of three types, namely: the **inductive effect**, the **resonance effect**, or the **field effect.** These are the ways in which electrical effects may be transmitted in molecules. When only single bonds are involved, the influence of the substituent is exerted mainly by the inductive effect, and when multiple bonds are involved, both inductive and resonance effects may come into play. The field effect operates across space and probably is less important than the inductive and resonance effects.

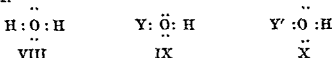
The inductive effect is essentially a displacement or shift of electrons in the molecule towards the electronegative radical. The effect drops off rapidly with distance. The resonance effect often promotes the establishment of electrical charges on atoms.

The relative acidic strengths of the acids of Table 16 can be explained in terms of the above concepts. Water ionizes to give equal amounts of hydrogen and hydroxyl ions, while YOH, ionizing in two ways, usually gives unequal amounts of these two ions.



$$\text{H—O—H} \rightleftharpoons \text{H}^+ + \text{OH}^-$$
$$\text{Y—O—H} \rightleftharpoons \text{H}^+ + \text{OY}^-$$
$$\text{Y—O—H} \rightleftharpoons \text{Y}^+ + \text{OH}^-$$

The operation of the inductive effect is shown schematically by VIII, IX, and X. When Y is electronegative relative to H (an electron-attracting radical) the electrical state, relative to water, VIII, may in a simplified fashion be represented by IX, whereas if Y′ is electropositive relative to H (an electron-repelling radical), the electrical state, relative to water, may be represented by X.

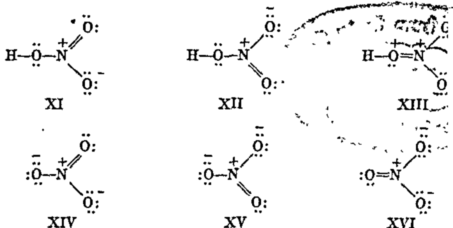


In VIII the valence electrons in the octet of oxygen are represented, in the interest of simplicity, as being equally attracted by oxygen and hydrogen. In IX the *strong attraction of Y for the electron pair (the first pair) means* the ionization to give hydroxide ion is diminished, for this shared electron pair must go with the oxygen atom in order to form hydroxide ion. On the other hand, the shift of this shared pair away from the oxygen atom increases the effective kernel charge of oxygen, owing to a decrease in the screening effect of this same pair. This results in increased attraction of the oxygen atom for the remaining six electrons, and allows the proton to leave more easily, since there is a lowered attraction between the second shared pair and the proton. The overall effect of an electronegative element or radical, therefore, is a decrease in the basic ionization and an increase in the acidic ionization.

Conversely, when Y′ is an electropositive atom or radical, the shift of electrons towards the oxygen atom, X, promotes basic ionization, because the oxygen atom can more easily take its shared-electron pair with it, to form hydroxide ion. At the same time, acidic ionization is depressed, owing to a decrease in the effective kernel charge of oxygen, with resultant decreased attraction for the remaining six electrons and a stronger attraction between the second shared pair and the proton. Generally radicals that increase acidic strength decrease basic strength, and *vice versa*.

When Y is neither strongly electronegative nor strongly electropositive, YOH ionizes weakly to give both H^+ and OH^- ions, and is amphoteric, much like water. Well-known examples are zinc hydroxide and stannous hydroxide.

Resonance may be more important than induction in determining the strength of YOH, and usually the two reinforce each other, as in the case of nitric acid, where both the inductive effect, as in IX above, and resonance effect increase acid strength. Resonance increases acid strength if the ion is stabilized by resonance more than the acid, and the greater this difference, the greater the degree of ionization. It is possible to write three resonance forms for nitric acid, *viz.*, XI, XII, and XIII, and three for nitrate ion, *viz.*, XIV, XV, and XVI.

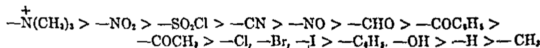


Whereas XIV, XV, and XVI are equally stable, and contribute alike to the structure of nitrate ion, XIII is very much less stable than XI and XII, because it violates the adjacent charge rule (p. 22). Thus its contribution to the overall structure of nitric acid is so small that essentially there are only two resonance forms. Owing to the greater number of equivalent forms, the resonance energy of nitrate ion is much greater than that of nitric acid, 45 kcal. compared to 25 kcal. per mole (Table 9, p. 21). The difference in stabilities causes the reaction to shift in the direction of the anion, and as a result nitric acid is a strong acid.

For any of the other acids in Table 16 the difference in the resonance energies of the acid and its anion is much less than in the case of nitric acid. Largely on this account they are weaker acids. The inductive effect of Y is an additional factor.

In organic molecules resonance may operate so as to place formal charges upon atoms that otherwise would be without formal charges. The presence of the charge may act in such a way as to retard or promote chemical reactivity. The relative inertness of vinyl chloride (Chap. 8) and the effect of substituents upon the reactivity of the benzene ring (Chap. 28) are typical examples of how resonance accounts for relative reactivities.

Radicals can be arranged in an approximate order of decreasing electronegativities. The order below is based upon a large amount of data, including the data of Table 16.



$$-\overset{+}{N}(CH_3)_3 > -NO_2 > -SO_2Cl > -CN > -NO > -CHO > -COC_6H_5 > -COCH_3 > -Cl, -Br, -I > -C_6H_5, -OH > -H > -CH_3$$

Physical and chemical properties of an organic compound usually are influenced by the nature of radicals present in the molecule. For example, electronegative radicals increase the acidic strength of acids and decrease the basic strength of bases, as with water. One of the aims of this text is the attempt to correlate the reactions of various types of organic compounds.

PROBLEMS

1. What deduction in regard to the arrangement of atoms in the molecule of each compound can be drawn from its electric dipole moment and how can the difference in the dipole moments of the two compounds be accounted for in terms of molecular structure and/or electronegativities?

a) boron trifluoride and phosphorus trichloride
b) methane (CH_4) and hydroxymethane
c) methane (CH_4) and monochloromethane
d) methane (CH_4) and nitromethane
e) tetrachloromethane and trichloromethane
f) carbon dioxide and sulfur dioxide
g) nitrous oxide and chlorine oxide
h) nitrous oxide and water
i) hydrogen bromide and hydrogen iodide
j) hydrogen iodide and hydrogen chloride
k) hydrogen iodide and iodomethane
l) phosphine and ammonia
m) hydrogen bromide and bromomethane
n) hydrogen sulfide and water
o) phosphorus trichloride and antimony trichloride
p) iodomethane and chloromethane
q) hydroxymethane and nitromethane
r) hydrogen cyanide and cyanomethane
s) silane and phosphine
t) trichloromethane and dichloromethane

2. Show by means of formulas how resonance is a factor in the ionization of the following, and make a comparison with nitric acid:

a) hypochlorous acid
b) sulfuric acid
c) nitrous acid
d) phosphoric acid
e) carbonic acid
f) sulfurous acid
g) perchloric acid
h) phosphorous acid
i) hydrogen peroxide

CHAPTER 4

Saturated Hydrocarbons, Alkanes, the Paraffin Series, C_nH_{2n+2}

Hydrocarbons are compounds of hydrogen and carbon only. They are classified on the bases of structure and chemical reactivity into two general types, the aliphatic (from the Greek, *aleiphatos*, meaning oil or fat) and the aromatic. The aliphatic hydrocarbons are subdivided further into saturated and unsaturated. The chemistry of saturated hydrocarbons, compared to the chemistry of unsaturated hydrocarbons and to other classes of organic compounds, is relatively simple. For that reason the study of organic chemistry usually starts with the saturated hydrocarbons which early were named paraffins, to indicate their chemical inertness (from the Latin, *parum affinis*, small affinity).

Other types of organic compounds contain one or more other elements, such as oxygen, nitrogen, sulfur, a halogen, etc. The properties, physical and chemical, of these types usually are different from those of hydrocarbons.

The paraffin hydrocarbons, the alkanes, are the simplest of the saturated hydrocarbons. They conform to a so-called **general formula**, in this case C_nH_{2n+2}. Here n is the number of carbon atoms. The alkanes are described first, and after them the unsaturated hydrocarbons. The simplest saturated hydrocarbon is methane.

Methane, CH_4, is the simplest hydrocarbon and is the first member of the paraffin series. It is a typically nonpolar substance (see Tables 11, 12, and 13). It is a colorless, odorless gas, soluble only to the extent of 1 cc. in 18 cc. of water, and in 2 cc. of alcohol. It is formed by the anaerobic fermentation of vegetable matter, a condition obtaining in marshes under water. The gas which rises to the surface of the water and escapes is a mixture of methane, carbon dioxide, and nitrogen. It is here known as marsh gas. The gas produced in the intestinal fermentation of imperfectly digested food contains at times more than 50 per cent of methane. The firedamp of the miners, which issues from seams in coal mines, is largely methane. Usually the destructive explosions to which coal mines are subject are due to methane.

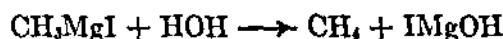
The two principal sources of methane are natural gas and artificial gas made from coal or oil. The gas issuing from oil (or gas) wells is largely methane, the percentage varying from 50 to 97. In California the usual content

is 85 to 88 per cent. Fuel gas is usually made by the destructive heating of coal or of petroleum oils. It is largely hydrogen and methane, the latter at times comprising as much as 50 per cent.

Methane usually is present in the gaseous portion of the decomposition products resulting from the "cracking," *i.e.*, the high temperature pyrolysis, of almost any petroleum product. This is because saturated hydrocarbons decompose at sufficiently high temperature into a variety of products, of which methane is one. If the temperature is high enough the final products are carbon, hydrogen, and methane.

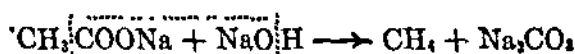
Preparation of Methane. In the laboratory, methane may be prepared in several ways, of which the first is the best since the operation can be carried out conveniently and a pure product is possible.

1. *From methyl magnesium iodide by the action of water (or alcohol)* (see Chap 9).



$$CH_3MgI + HOH \longrightarrow CH_4 + IMgOH$$

2. *By heating anhydrous sodium acetate and soda lime.*



$$CH_3COONa + NaOH \longrightarrow CH_4 + Na_2CO_3$$

3. *By reduction of many one-carbon compounds containing halogen or oxygen.* Thus the iodine atom in methyl iodide may be replaced by hydrogen either through the use of metallic zinc in the presence of sulfuric acid, or by heating with hydriodic acid and phosphorus. In this case the reducing agent is phosphorus. Carbon monoxide and carbon dioxide are catalytically reduced to methane in the presence of finely divided nickel at 200 to 250°.



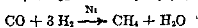
$$2\,CH_3I + 2\,Zn + H_2SO_4 \longrightarrow 2\,CH_4 + ZnSO_4 + ZnI_2$$



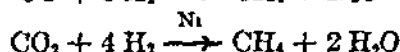
$$CH_3I + HI \rightleftharpoons CH_4 + I_2$$



$$3\,I_2 + 2\,P + 6\,H_2O \longrightarrow 2\,H_3PO_3 + 6\,HI$$



$$CO + 3\,H_2 \xrightarrow{Ni} CH_4 + H_2O$$



$$CO_2 + 4\,H_2 \xrightarrow{Ni} CH_4 + 2\,H_2O$$

4. *By direct union of carbon and hydrogen in the presence of a nickel catalyst* (see Pyrolysis of Methane).

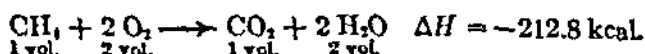


$$C + 2\,H_2 \longrightarrow CH_4$$

This is a direct synthesis of methane from the elements. Any synthesis from the elements is called a **total synthesis**. It may be direct as in this case, but usually is indirect.

Reactions of Methane. In general methane is inert. It does not react at ordinary temperatures with acids, bases, oxidizing agents, or reducing agents. In addition to its decomposition when heated, described later, the principal reactions of methane are oxidation and halogenation.

1. *Complete oxidation in an excess of oxygen or air* (*combustion*).

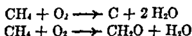


$$\underset{1\text{ vol.}}{CH_4} + \underset{2\text{ vol.}}{2\,O_2} \longrightarrow \underset{1\text{ vol.}}{CO_2} + \underset{2\text{ vol.}}{2\,H_2O} \quad \Delta H = -212.8\text{ kcal.}$$

Methane burns when ignited in oxygen or air, and the reaction is highly exothemic to the extent of 212.8 kcal. per mole of methane. Mixtures of air with 5 to 14 per cent of methane explode when ignited. **The heat of combustion** of methane is 212.8 kcal. The reaction is important industrially as a source of heat or power.

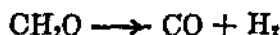
The volumetric relations in the reaction mentioned above form the basis of an analytical method. If the measurements of initial and final volumes are made at a temperature above 100°, there is no change in volume. If they are made, after the gases have been thoroughly dried, at room temperature, the final volume is one-third the initial volume; thus the observed contraction in volume is twice the initial volume of methane. Moreover, the contraction in volume next observed when a strong base is added equals the initial volume of methane, for one volume of carbon dioxide is formed from each volume of methane.

2. *Partial oxidation in a deficiency of oxygen or air.* Carbon is formed in a finely divided state when a flame of ignited methane impinges on a cold surface. Formaldehyde is formed by high temperature oxidation (500–750°) without ignition.



$$CH_4 + O_2 \longrightarrow C + 2\,H_2O$$
$$CH_4 + O_2 \longrightarrow CH_2O + H_2O$$

But since formaldehyde rapidly decomposes at these high temperatures the main oxidation product is carbon monoxide (see Chap. 17).



$$CH_2O \longrightarrow CO + H_2$$

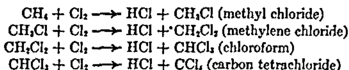
3. *Decomposition with fluorine or chlorine.* Fluorine reacts vigorously even in the dark, yielding mainly hydrogen fluoride, carbon, and carbon tetrafluoride. Methane burns in chlorine (when ignited).



$$CH_4 + 2\,Cl_2 \longrightarrow C + 4\,HCl$$

The reaction takes place explosively when a mixture of the two gases is ignited, or illuminated by sunlight. The carbon is in a finely divided condition and is suitable for use as carbon black. It must be freed of chlorinated products, formed by side reactions.

4. *Substitution with chlorine or bromine.* By proper control of conditions (temperature, concentrations) the decomposition reaction above with chlorine can be eliminated. By illumination, or by the use of suitable catalysts, the following reactions of **substitution** can be accelerated.



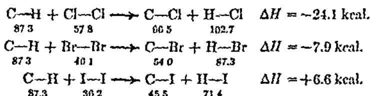
$$CH_4 + Cl_2 \longrightarrow HCl + CH_3Cl \text{ (methyl chloride)}$$
$$CH_3Cl + Cl_2 \longrightarrow HCl + CH_2Cl_2 \text{ (methylene chloride)}$$
$$CH_2Cl_2 + Cl_2 \longrightarrow HCl + CHCl_3 \text{ (chloroform)}$$
$$CHCl_3 + Cl_2 \longrightarrow HCl + CCl_4 \text{ (carbon tetrachloride)}$$

The first reaction product, methyl chloride, CH_3Cl, can be obtained in satisfactory yield when methane is in large excess, and the last reaction product, carbon tetrachloride, when chlorine is in excess. Effective catalysts for the

reaction are anhydrous metallic chlorides such as ferric chloride and aluminum chloride. They favor the higher chlorinated products. The chlorination reactions are important industrially in the preparation of the four chlorinated methanes.

Substitution. When chlorine reacts with methane to produce methyl chloride and hydrogen chloride, a chlorine atom is said to be substituted for a hydrogen atom, and the change is called a substitution. A similar statement holds for each of the subsequent reactions. These chlorine-containing compounds, or chlorinated products, are all substitution products of methane and are named as such: methyl chloride is a monochlorine substitution product of methane and is called chloromethane; methylene chloride is a dichlorine substitution product and is called dichloromethane. Also, chloroform is called trichloromethane, and carbon tetrachloride, tetrachloromethane. Methane reacts also with bromine, yielding hydrogen bromide and analogous brominated methanes, but it reacts only slightly with iodine. Many higher hydrocarbons, especially aromatic, undergo reactions in which other groups, such as the nitro and sulfo groups, are substituted for hydrogen atoms. Substitution reactions are typical reactions of hydrocarbons.

Energy Changes in Substitution Reactions. When methane and chlorine react to produce methyl chloride and hydrogen chloride, two bonds are broken *viz.*, C—H and Cl—Cl, and two new bonds are formed, *viz.*, C—Cl and H—Cl. Energy must be supplied in order to break the first two bonds and a certain amount of energy is given up when the last two bonds are formed. The overall effect, expressed as calories, is the heat of the reaction. From the known values of the bond energies (Table 7, p. 17) it is possible to calculate the energy changes for the following gaseous reactions in the gaseous state,



$$\underset{87.3}{\text{C—H}} + \underset{57.8}{\text{Cl—Cl}} \longrightarrow \underset{66.5}{\text{C—Cl}} + \underset{102.7}{\text{H—Cl}} \quad \Delta H = -24.1 \text{ kcal.}$$

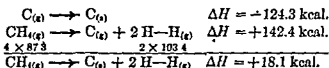
$$\underset{87.3}{\text{C—H}} + \underset{46.1}{\text{Br—Br}} \longrightarrow \underset{54.0}{\text{C—Br}} + \underset{87.3}{\text{H—Br}} \quad \Delta H = -7.9 \text{ kcal.}$$

$$\underset{87.3}{\text{C—H}} + \underset{36.2}{\text{I—I}} \longrightarrow \underset{45.5}{\text{C—I}} + \underset{71.4}{\text{H—I}} \quad \Delta H = +6.6 \text{ kcal.}$$

Thus the first two reactions are exothermic, and the third, endothermic. It is interesting to compare these values with similar data in the reactions of the halogens with hydrogen. Doubling the ΔH values of Table 10 (p. 24), since they are based upon $\frac{1}{2}X_2$, the values are -44, -17.2, and $+12.8$ kcal. Although the data are not strictly comparable, since the values of Table 10 are calculated for liquid bromine and solid iodine, nevertheless, the general relationships are the same. Thus the equilibrium conditions that exist in connection with the hydrogen halides would be expected to hold approximately in substitution reactions with the halogens. Chlorine and bromine react essentially completely, but iodine only slightly.

Pyrolysis of Methane. Methane is the most stable of the paraffin hydrocarbons. It is stable at the ordinary temperature and is not changed

when heated for six days at 480°. At temperatures between 650° and 700° a slow decomposition sets in. This takes place more rapidly at higher temperatures or in the presence of finely divided metallic nickel, which catalyzes the reaction. The products are carbon and hydrogen. The reaction therefore is a reversal of the reaction by which methane is formed from the elements. The energy change at room temperature can be approximated from bond energy values by taking into account the heat of sublimation of graphite, which is 124.3 kcal. per gram atom.



$$\begin{array}{ll} C_{(g)} \longrightarrow C_{(s)} & \Delta H = -124.3 \text{ kcal.} \\ \underset{4 \times 87.3}{CH_{4(g)}} \longrightarrow C_{(g)} + \underset{2 \times 103.4}{2\,H\text{—}H_{(g)}} & \Delta H = +142.4 \text{ kcal.} \\ \hline CH_{4(g)} \longrightarrow C_{(s)} + 2\,H\text{—}H_{(g)} & \Delta H = +18.1 \text{ kcal.} \end{array}$$

Thus, if a catalyst were available that could cause a reaction to take place at 25° in a mixture of methane, graphite, and hydrogen, it is easy to see that it would proceed to the *left*, not the right, since the reaction is exothermic in that direction, *i.e.*, ΔH is -18.1 kcal. Actually, no sufficiently powerful catalyst is known. When the temperature of the system is raised, the position of equilibrium would be expected to shift in favor of the reaction towards the *right*, if a reaction could be made to take place, since energy is absorbed in this direction. This follows from the principle of Le Chatelier, which states that when a system in equilibrium is subjected to some stress, the equilibrium tends to shift in the direction which relieves the stress. Measurements have been made on equilibria at higher temperatures in the presence of a nickel catalyst. The data in Table 17 show that the equilibrium does shift, and

TABLE 17 | **Equilibrium Mixtures of Methane and Hydrogen in Contact with Graphite and Nickel**

Temperature, ° C.	**500**	**600**	**780**	**900**	**1000**	**1100**
Methane, per cent	*62.5*	*31.7*	*10*	*4.7*	*1.1*	*0.6*
Hydrogen, per cent	37.5	68.3	90	95.3	98.9	99.4

that at a sufficiently high temperature methane decomposes almost completely into carbon and hydrogen. However, other reactions take place simultaneously but more slowly, and these lead to the formation of ethylene and other hydrocarbons. From these data the free energy of formation of methane from the elements at 25° and one atmosphere has been calculated as $\Delta F = -11.58$ kcal. Thus even in this heterogeneous system ΔH and ΔF are not greatly different (-18.1 and -11.6 kcal., respectively).

The decomposition of methane is the main reaction in the "reforming" of natural gas, *i.e.*, its partial pyrolysis at high temperature. This is done to obtain a mixture of methane and hydrogen having a calorific value close to that of illuminating gas obtained from coal or oil.

Structure of Methane. In 1874 Le Bel and van't Hoff independently advanced the theory that four atoms or groups attached to a carbon atom are

arranged at tetrahedral corners about the carbon atom. Since that time a wealth of experimental evidence in substantiation of the theory has accumulated. Significant are the experimentally determined dipole moment, $\mu = 0$ (Table 11, p. 28) and bond angles of 109° 28′ (Table 6, p. 14). The four hydrogen atoms are attached to the carbon atom by electron-pair bonds and the angle between any pair of valence bonds is the tetrahedral angle of 109° 28′. (Fig. 6; refer also to Fig. 3, p. 15.)

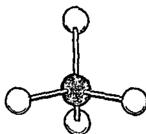
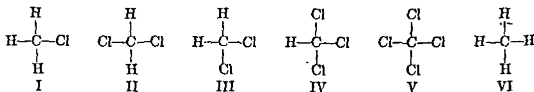


Figure 6 • The Methane Molecule

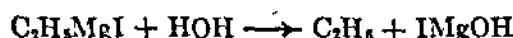
A planar structure of methane could have zero moment also. In this the four hydrogen atoms would be arranged at the four corners of a square, with the carbon atom in the center. However, the tetrahedral structure accounts for the fact that only four substitution products — one monochloro, I; one dichloro, II; one trichloro, IV; and one tetrachloro, V — are known; whereas on the basis of a planar structure, two dichloromethanes, II and III, are possible.



Therefore II and III are identical, not different. They merely represent two ways of projecting on a plane surface the three-dimensional formula of dichloromethane, CH_2Cl_2. It is convenient to represent the structures of most organic compounds by means of **projection formulas.** Thus methane usually is represented by VI. However, sometimes the arrangement of groups in space about carbon atoms must be taken into account (see stereoisomerism, Chaps 5, 18).

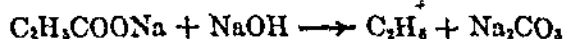
Ethane, C_2H_6, occurs in solution in petroleum, and also as a constituent of natural gas, usually to the extent of 5 to 10 per cent. In a few cases, as in Kentucky, this may be as high as 65 per cent. Ethane may be prepared analogously to methane (1), (2), and (3), or by other methods (4) and (5). Method (1) is superior, because of convenience and the purity of the product.

1. *From ethyl magnesium iodide* (see Chap. 9).



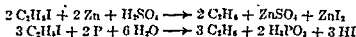
$$C_2H_5MgI + HOH \longrightarrow C_2H_6 + IMgOH$$

2. *By heating sodium propionate with soda lime.* Other gases are present, ethylene in particular, due to side reactions.



$$C_2H_5COONa + NaOH \longrightarrow C_2H_6 + Na_2CO_3$$

3. *By reduction of ethyl iodide with zinc, or with hydriodic acid and phosphorus.*



$$2\,C_2H_5I + 2\,Zn + H_2SO_4 \longrightarrow 2\,C_2H_6 + ZnSO_4 + ZnI_2$$
$$3\,C_2H_5I + 2\,P + 6\,H_2O \longrightarrow 3\,C_2H_6 + 2\,H_3PO_3 + 3\,HI$$

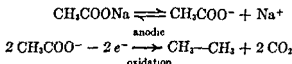
4. *From methyl iodide and metallic sodium (Wurtz synthesis).* This is important in relation to the structure of methane.



$$2\,CH_3I + 2\,Na \longrightarrow H_3C{-}CH_3 + 2\,NaI$$

The mechanism of the reaction is not so simple as indicated above. It is believed that an intermediate is methyl sodium, CH_3Na (Chap. 9), and this reacts with methyl iodide to form the final products. The reaction may be carried out with the corresponding methyl bromide, CH_3Br, or methyl chloride, CH_3Cl, but less easily, since the iodide is the most reactive, the chloride the least.

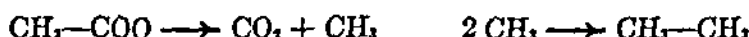
5. *By the electrolysis of sodium acetate.*



$$CH_3COONa \rightleftharpoons CH_3COO^- + Na^+$$

$$2\,CH_3COO^- - 2\,e^- \xrightarrow[\text{oxidation}]{\text{anodic}} CH_3{-}CH_3 + 2\,CO_2$$

Here the anion loses its negative charge at the anode, and is converted into the unstable free acetate radical. This is believed to decompose into carbon dioxide and the **free methyl radical,** two of which combine to form the *ethane molecule.*



$$CH_3{-}COO \longrightarrow CO_2 + CH_3 \qquad 2\,CH_3 \longrightarrow CH_3{-}CH_3$$

6. *By the catalytic hydrogenation of ethylene* (Chap. 5).

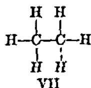


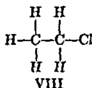
$$C_2H_4 + H_2 \longrightarrow C_2H_6 \quad \Delta H = -29.8\text{ kcal.}$$

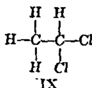
From bond energies ΔH of hydrogenation at room temperature is -29.8 kcal. per mole. One would expect the equilibrium to lie far to the right.

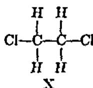
Ethane like methane is a typically nonpolar substance. In Table 20 (p. 50) are listed some of its properties. In chemical reactivity it resembles methane. It can be chlorinated, and any or all of the hydrogen atoms may be replaced by chlorine. The monochlor and dichlor substitution products are important (Chap. 8).

Structure and Substitution Products of Ethane. On the basis of two of the synthetic methods, (4) and (5) above, ethane would appear to be composed of two methyl radicals, VII.









If this is the case, then according to structural theory only one monochloro substitution product is possible, VIII, since all six hydrogen atoms are equivalent, *i.e.*, they all bear the same relationship to the molecule as a whole. One must visualize the molecules in three dimensions, with the four valences of

the carbon atom directed towards the four corners of a tetrahedron. The formulas above are merely projection formulas. There is only one ethyl chloride, C_2H_5Cl. There is agreement between prediction and fact in this case.

There are two dichloroethanes possible, $C_2H_4Cl_2$, since in ethyl chloride the hydrogen atoms are *not* equivalent. According to structural theory there should be these two possibilities, 1,1-dichloroethane, IX, and 1,2-dichloroethane, X. Actually there are just these two dichloroethanes; also there are just two dibromoethanes and two diiodoethanes. In these cases also there is agreement between prediction and the actual number of compounds.

Isomerism. When two or more compounds have the same molecular formula, for example $C_2H_4Cl_2$ in the case of the two dichloroethanes, the compounds are called isomers (Gr. *isos*, equal, + *meros*, part), and the phenomenon is called isomerism. The difference between the two compounds can be shown by means of structural formulas, which may either be **graphic formulas**, like those shown above, IX and X, or **condensed** structural formulas, CH_3—$CHCl_2$ and $ClCH_2$—CH_2Cl, respectively. The isomerism of the dichloroethanes sometimes is called **position isomerism**, indicating a difference in the relative position on the chain of carbon atoms.

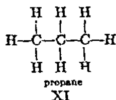
Propane, C_3H_8, like ethane is present in natural gas, but to a smaller extent. It is a by-product from natural gasoline. Its preparation from methyl iodide, ethyl iodide, and metallic sodium throws light upon its structure.



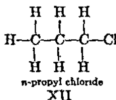
$$CH_3I + 2\,Na + IC_2H_5 \longrightarrow CH_3\text{—}C_2H_5 + 2\,NaI$$

Two other products are formed at the same time; ethane and butane. The main reaction of propane is that of chlorination, as in the case of ethane.

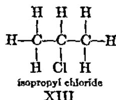
Structurally, propane may be considered to be the methyl derivative of ethane, *i.e.*, a methyl group, CH_3— is written in the place of one of the hydrogen atoms of ethane, XI.



propane
XI



n-propyl chloride
XII



isopropyl chloride
XIII

It is evident that of the eight hydrogen atoms six are equivalent and two are different from these but equivalent to each other. Thus on the basis of structural theory two monochloro substitution products of propane are predicted, XII and XIII. There are just these two known.

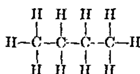
Alkyl Radicals. Methyl, CH_3, is the univalent radical of methane, CH_4, and ethyl, C_2H_5, is the univalent radical of ethane, C_2H_6, the name of the radical being derived from *the hydrocarbon by changing the ending -ane to -yl*. The univalent radicals of the alkanes have the general formula C_nH_{2n+1} and are called alkyl radicals. Although there is only one methyl or one ethyl

radical, there are two propyl radicals, *viz.*, normal propyl, $CH_3CH_2CH_2$, and isopropyl, $(CH_3)_2CH$, corresponding to the two monochloropropanes above. There are more than two butyl, pentyl, hexyl, etc., radicals. Continual use is made of names of radicals, especially methyl and ethyl, in the naming of organic compounds, such as methyl iodide, CH_3I, ethyl bromide, C_2H_5Br, ethyl alcohol, C_2H_5OH, ethylamine, $C_2H_5NH_2$, methyl sulfide, $(CH_3)_2S$, etc. Radicals, with few exceptions, exist combined in compounds, not in the free state.

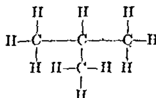
Free Radicals. The discovery of ethane was the result of the attempt about the middle of the nineteenth century to isolate the free, or uncombined, radicals of which organic compounds were believed to be constituted. Kolbe, who first carried out the electrolysis of sodium acetate solutions, believed that he had actually isolated the methyl radical, for the gas collected at the anode appeared to have the formula CH_3, as determined by analysis. But later, following the general acceptance of Avogadro's hypothesis, revived by Cannizzaro, the molecular weight determination of the gas showed that the formula had to be doubled, that is, C_2H_6. All attempts made in the succeeding five decades to isolate free radicals were fruitless, because aliphatic free radicals exist only momentarily (tetramethyllead, Chap. 9). The first free radical, triphenylmethyl, $(C_6H_5)_3C$, was discovered by Gomberg in 1900 (Chap. 37).

The spontaneous formation of free radicals from a gaseous hydrocarbon at the ordinary temperature is quite improbable because 85 kcal. must be supplied in order to break the C—C bond. It is only at fairly high temperatures that such a decomposition takes place (p. 55).

Butane, C_4H_{10} is methylpropane. Two butanes are predictable on the basis of the structural theory, and two are known. They are called normal butane, XIV, and isobutane, XV.



normal butane
XIV



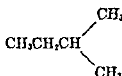
isobutane
XV

These may be regarded as derived from propane by the substitution of a methyl radical for a hydrogen atom. These hydrocarbons are present in natural gas and in petroleum, the normal isomer predominating. A mixture is obtained as a by-product in the stabilizing of natural gasoline. Isobutane is important in the manufacture of synthetic gasoline. The pure hydrocarbons may be prepared by synthesis. (See general methods of preparation.)

Pentane, C_5H_{12}, is methylbutane. If the different hydrogen atoms of normal and isobutane are replaced by methyl radicals, one might expect four compounds, as follows:

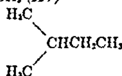
from $CH_3CH_2CH_2CH_3$ (XIV)

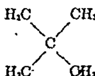




XVI XVII

from $(CH_3)_2CHCH_3$ (XV)





XVIII XIX

Actually, three and only three pentanes are known. Inspection of the above formulas shows that XVII and XVIII are identical and that the theory, therefore, predicts three and only three isomeric pentanes. Fact and theory therefore are in agreement. The pentanes occur in petroleum and natural gas. Natural gasoline is composed largely of normal pentane and isopentane (see Table 19, for nomenclature and physical properties).

A carbon atom at the end of a carbon chain is called a **primary** carbon atom since it is joined to only one other carbon atom. One joined to two other carbon atoms is called a **secondary**, to three others a **tertiary**, and to four others a ***quaternary*** carbon atom.

Isomerism in the Paraffin Series. Above pentane the number of isomers which are possible according to structural theory increases rapidly. All of the structurally isomeric hydrocarbons up to and including the octanes have been prepared and their properties determined. Many higher ones are known also. In Table 18 are listed the number of such isomers, calculated by a complicated procedure. This does not include stereoisomeric forms.

TABLE 18 | Calculated Number of Structurally Isomeric Paraffin Hydrocarbons

CARBON CONTENT	NO ISOMERS	CARBON CONTENT	NO ISOMERS	CARBON CONTENT	NO. ISOMERS
1	1	9	35	17	24,894
2	1	10	75	18	60,523
3	1	11	159	19	147,289
4	2	12	355	20	366,319
5	3	13	802	25	3.68×10^7
6	5	14	1,858	30	4.11×10^9
7	9	15	4,347	40	6.25×10^{13}
8	18	16	1,0359		

Nomenclature of Hydrocarbons. There are three important ways of naming hydrocarbons:

1. The common (trivial) name, from the formula; the isomer having the

so-called straight chain (no branching) is called the normal hydrocarbon; the one having a branched chain at one end only, $\begin{matrix}C\\ \\ C\end{matrix}\!\!>\!C—$, the rest of the chain being normal, is called the iso; other isomers must be designated by other prefixes. This method is satisfactory for butanes and pentanes.

2. From methane; that carbon is selected as the methane carbon atom to which the most substituent radicals are joined; the compound is then named as a substitution product of methane. This method is not satisfactory for the higher hydrocarbons when the radicals cannot be conveniently named.

3. In 1892 a rational nomenclature of aliphatic compounds was adopted by the International Chemical Congress at Geneva. In 1930 at Liege the Council of the International Union of Chemistry recommended improvements and extension of this method of nomenclature, which will be referred to as the I.U.C. system of nomenclature in this text.

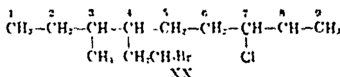
Hydrocarbons of the paraffin series are called alkanes. The basic name of any alkane is that of the longest chain of primary and secondary carbon atoms, that is, the **normal** chain. For example *n*-pentane, C_5H_{12} (Table 19), is simply pentane. The carbon atoms are designated by number, starting at one end and numbering consecutively. The position of an alkyl radical, or **side chain,** on the main carbon chain is indicated by the proper number, either before or after the name of the radical. The number assigned should be as low as possible. If two or more side chains are present, the order may be alphabetical, or based on size, the smallest first. In Table 19 are names of the butanes and pentanes.

TABLE 19 | **Nomenclature of Butanes and Pentanes**

FORMULA	M.P. °C	B.P. °C	NAME		
			common	substituted methane	I.U.C. system
$CH_3CH_2CH_2CH_3$	−135	−0.6	normal butane	methylethylmethane	butane
$(CH_3)_2CHCH_3$	−145	−12.2	isobutane	trimethylmethane	2-methylpropane
$CH_3(CH_2)_3CH_3$	−130	36.0	normal pentane	diethylmethane	pentane
CH_3 | $CH_3CHCH_2CH_3$	−160	27.9	isopentane	dimethylethylmethane	2-methylbutane
CH_3 | CH_3CCH_3 | CH_3	−17	9.5	neopentane	tetramethylmethane	2,2-dimethylpropane

In naming halogen derivatives of alkanes, the hydrocarbon should be named first. After this is decided on, the name of the halogen atom is placed before the name of the hydrocarbon and the number indicating its position on the carbon chain is placed ahead of its name.

In case a side chain carries substituents, the carbon atoms of the side chain are numbered, starting next to the main chain and the position of the substituents indicated in the usual way. The entire side chain is inclosed in parentheses. Thus XX is called 7-chloro-3-methyl-4-(2-bromoethyl)-nonane



XX

Homologous Series; Homology. In Table 20 are listed alkanes having the normal structure, *i.e.*, no side chains. They are the normal alkanes (paraffins). Each successive member through eicosane differs from the one

TABLE 20 | **Normal Alkanes**

HYDROCARBON	FORMULA	M.P., °C	B.P., °C, AT 760 MM.	D_4^{20}	n_D^{20}
Methane	CH_4	−182.6	−161.58	0.4240 [a]	
Ethane	CH_3CH_3	−172.0	−88.5	.5462 [a]	
Propane	$CH_3CH_2CH_3$	−187.1	−42.2	.5824 [a]	
Butane	$CH_3(CH_2)_2CH_3$	−135.0	−0.5	.5788	
Pentane	$CH_3(CH_2)_3CH_3$	−129.7	36.0	.6263	1.3577
Hexane	$CH_3(CH_2)_4CH_3$	−95.4	68.7	.6594	1.3751
Heptane	$CH_3(CH_2)_5CH_3$	−90.5	98.4	.6838	1.3877
Octane	$CH_3(CH_2)_6CH_3$	−56.8	125.6	.7028	1.3976
Nonane	$CH_3(CH_2)_7CH_3$	−53.7	150.7	.7178	1.4056
Decane	$CH_3(CH_2)_8CH_3$	−29.7	174.0	.7300	1.4120
Undecane	$CH_3(CH_2)_9CH_3$	−25.6	195.8	.7402	1.4173
Dodecane	$CH_3(CH_2)_{10}CH_3$	−9.6	216.2	.7493	1.4219
Tridecane	$CH_3(CH_2)_{11}CH_3$	−6	234	.7568	
Tetradecane	$CH_3(CH_2)_{12}CH_3$	5.5	252	.7636	
Pentadecane	$CH_3(CH_2)_{13}CH_3$	10	266	.7688	1.430
Hexadecane	$CH_3(CH_2)_{14}CH_3$	18.1	280	.7749	1.4352
Heptadecane	$CH_3(CH_2)_{15}CH_3$	22.0	292	.7767 [b]	1.4360 [b]
Octadecane	$CH_3(CH_2)_{16}CH_3$	28.0	308	.7767 [b]	1.4367 [b]
Nonadecane	$CH_3(CH_2)_{17}CH_3$	32	320	.7776 [b]	
Eicosane	$CH_3(CH_2)_{18}CH_3$	36.4	205 [c]	.7777 [b]	
Pentacosane	$CH_3(CH_2)_{23}CH_3$	53.3	259 [c]	.7785 [b]	
Tricontane	$CH_3(CH_2)_{28}CH_3$	66	304 [c]	.7797 [b]	
Pentatriacontane	$CH_3(CH_2)_{33}CH_3$	74.6	331 [c]	.7814 [b]	
Hexacontane	$CH_3(CH_2)_{58}CH_3$	99	250 [d]		

[a] At b.p.
[b] At m.p.
[c] At 15 mm.
[d] At 10[illegible] mm.

preceding by having a methyl group, CH_3, in place of one of the hydrogen atoms. In this series each successive methyl group is attached to a terminal carbon atom. The compounds in this table constitute a typical homologous series. It is characteristic of all homologous series that the molecular weight of any one compound exceeds by fourteen the molecular weight of the next lower member of the series, since their formulas differ by CH_2 (methylene).

In the homologous series of the normal paraffins some physical properties change fairly regularly as the molecular weights increase. This is true in a general way of melting point, boiling point, and specific gravity. The first four members are colorless gases at ordinary temperature and pressure, the next thirteen are colorless liquids, and those of higher molecular weight are solids. The melting points are less regular than the boiling points, for the former decrease at first, then increase. The third member of the series, propane, has the lowest melting point. Above propane the melting points increase, but not at a constant rate, since the jump from an odd-numbered to an even-numbered hydrocarbon is always greater than the neighboring jumps of opposite kind. The boiling points go up with increase in molecular weight and change more regularly than the melting points do. The boiling point difference between successive members drops off with increase in molecular weight and is approximately 20° over a considerable range. The specific gravities increase rapidly at first, less rapidly later on, and finally become fairly constant at about 0.8.

In regard to other physical properties the members of the homologous series of hydrocarbons are much alike. They are typical nonpolar compounds of zero dipole moment (Table 11), low dielectric constant (Table 12, p. 30), very low conductivity, and no ionizing power. The liquid members are insoluble in water, soluble in many organic solvents such as ether and acetone, and completely miscible with each other. In chemical reactivity also the paraffin hydrocarbons are much alike.

The similarity in the structures and in the properties of a group of compounds, such as the members of the homologous series of the paraffin hydrocarbons, is known as **homology.** The principle of homology is an aid in the study of organic chemistry because the general relationship between structure and properties which holds in the paraffin series is true also of other homologous series such as the olefins, the alcohols, and the acids. The members of any one homologous series in general react more or less alike chemically. The reactions that they undergo are known as class reactions or as general reactions for that particular homologous series.

General Methods of Preparing Alkanes. Alkanes may be prepared by the following general methods. Here R represents an alkyl radical, C_nH_{2n+1}.

1. *Decomposition of an alkyl magnesium halide* (Grignard reagent) with water or alcohol (Chap. 9).



$$RMgX + HOH \longrightarrow R{-}H + XMgOH$$

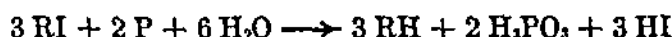
This method is much used since Grignard reagents usually are easily prepared. The above reaction proceeds rapidly with good yields and the products are reasonably pure.

2. *Reduction of an alkyl halide* (preferably iodide) by the zinc-copper couple and alcohol.



$$RI + Zn + C_2H_5OH \longrightarrow RH + IZnOC_2H_5$$

3. *Reduction of an alkyl iodide* by heating with hydriodic acid and red phosphorus in a sealed tube.



$$3\,RI + 2\,P + 6\,H_2O \longrightarrow 3\,RH + 2\,H_3PO_3 + 3\,HI$$

Hydriodic acid reduces part of the alkyl iodide. Phosphorus reduces the iodine formed (see preparation of methane) to hydriodic acid. The method is not used much at this time.

4. *The Wurtz synthesis.*



$$2\,RX + 2\,Na \longrightarrow R{-}R + 2\,NaX$$

By this method a single alkyl halide yields a fairly pure paraffin. A mixture of two alkyl halides yields three hydrocarbons. However, side reactions may take place.

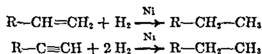
5 *Electrolysis of salts of organic acids* (Kolbe synthesis).



$$2\,RCOO^- - 2\,e^- \longrightarrow R{-}R + 2\,CO_2$$

This method is of historical interest, for it was early applied to the preparation of paraffin hydrocarbons. Side reactions often result in the formation of unsaturated hydrocarbons.

6. *Catalytic hydrogenation of alkenes* (Chap. 5) *or alkynes* (Chap. 6).



$$R{-}CH{=}CH_2 + H_2 \xrightarrow{Ni} R{-}CH_2{-}CH_3$$

$$R{-}C{\equiv}CH + 2\,H_2 \xrightarrow{Ni} R{-}CH_2{-}CH_3$$

This is a valuable method, since alkenes and alkynes generally, besides the ones indicated above, can be obtained quite pure by a variety of methods and the hydrogenation proceeds quantitatively, usually yielding pure products.

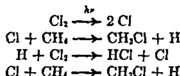
General Reactions of Alkanes. The alkanes are noted for their chemical inertness and nonreactivity, for under ordinary conditions they are not altered by the action of metals, alkalies, dilute aqueous acids, reducing agents, or most of the oxidizing agents. They undergo substitution by chlorine and, slowly, by bromine. However, at elevated temperatures it is possible to carry out other reactions, and within recent years these have become increasingly important from an industrial standpoint. These are mainly nitration, oxidation, dehydrogenation, decomposition, isomerization, alkylation, and cyclization. Some of the reactions such as oxidation, substitution, and isomerization can be carried out conveniently in the laboratory, while others, such as dehydrogenation, decomposition, and cyclization require elaborate equipment

1. *Combustion.* Complete combustion to carbon dioxide and water in an excess of oxygen or of air is characteristic of the lower members, which can be analyzed this way by the methods of gas analysis. Complete combustion of the higher members becomes progressively more difficult and often is accompanied by formation of carbon. Combustion is of great importance as a source of heat, power, or light (natural gas, gasoline, kerosene, fuel oil, etc.)

Partial oxidation of hydrocarbons with an amount of air insufficient for complete oxidation may lead to the formation of carbon black (see Methane) or of many oxygenated compounds such as aldehydes and acids. One method is the passage of a mixture of hydrocarbon gas and air through a heated zone, either alone or in the presence of a suitable catalyst as, for example, the oxides of nitrogen or metallic copper or silver.

2. *Halogenation.* Chlorination with chlorine may be carried out under a variety of conditions as, for example, illumination, heating, or in the presence of catalysts. Light of short wave length such as violet or ultraviolet is more effective than light of longer wave length. Lower hydrocarbons up to and including the pentanes are chlorinated industrially. Mixtures of isomeric products result from hydrocarbons above ethane (see Chap. 8, Halogen Compounds).

Bromination of liquid hydrocarbons with liquid bromine proceeds with reasonable rapidity under illumination. The product usually is a mixture of mono, di, and higher halogenated compounds. Chlorination and bromination in the light are free radical reactions. Light causes dissociation of the halogen molecule into free radicals (atoms) and these can initiate chain reactions.



$$Cl_2 \xrightarrow{h\nu} 2\,Cl$$
$$Cl + CH_4 \longrightarrow CH_3Cl + H$$
$$H + Cl_2 \longrightarrow HCl + Cl$$
$$Cl + CH_4 \longrightarrow CH_3Cl + H$$

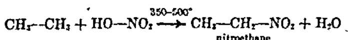
Once started, a chain reaction continues until terminated, as by combination of two free radicals.

Chlorination of liquid hydrocarbons can be accomplished conveniently by heating with sulfuryl chloride in the *dark*, with a small amount of an organic peroxide as catalyst.



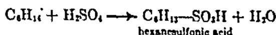
$$C_6H_{14} + SO_2Cl_2 \longrightarrow C_6H_{13}Cl + HCl + SO_2$$

3. *Nitration and sulfonation.* Nitration of liquid alkanes can be accomplished by heating with nitric acid. The reaction is slow and is accompanied by oxidation. In general the yields are low and unsatisfactory. The nitration proceeds best at a tertiary carbon atom. Recently an industrial process has been develeped in which the nitration of methane and higher alkanes is carried out in the gas phase at elevated temperature (see Nitroparaffins, Chap. 24).



$$CH_3\text{—}CH_3 + HO\text{—}NO_2 \xrightarrow{350\text{–}500^\circ} \underset{\text{nitroethane}}{CH_3\text{—}CH_2\text{—}NO_2} + H_2O$$

Sulfonation by means of fuming sulfuric acid is slow, and takes place best at a tertiary carbon atom. It is attended by oxidation. The yields are low:



$$C_6H_{14} + H_2SO_4 \longrightarrow \underset{\text{hexanesulfonic acid}}{C_6H_{13}\text{—}SO_3H} + H_2O$$

Better results are obtained with sulfuryl chloride under illumination.



$$C_6H_{14} + SO_2Cl_2 \longrightarrow \underset{\text{hexanesulfonyl chloride}}{C_6H_{13}\text{—}SO_2Cl} + HCl$$

4. *Dehydrogenation and decomposition.* On pyrolysis at high temperatures, loss of hydrogen and decomposition usually take place simultaneously. The complicated series of reactions which take place usually is called **cracking**, from the peculiar sound which accompanies the decomposition of high boiling liquids, for example kerosene, when they are distilled.

Ethane is less stable than methane and begins to decompose at 485° in the absence of catalysts, mainly to ethylene and hydrogen.



$$C_2H_6 \longrightarrow C_2H_4 + H_2$$

This is the reverse of the reaction by which ethane can be obtained from ethylene. At 25° in the presence of a very active catalyst the equilibrium lies well to the left (see preparation of ethane). Because the reaction as written above is strongly endothermic, the equilibrium here, as in the case of methane, shifts to the right at higher temperatures. Between 550° and 700°, the gases are in equilibrium, but this is not a true equilibrium since methane also is formed by a slow decomposition reaction. At 750° in one hour ethane is completely decomposed. The main products are methane and hydrogen. Ethylene is a minor constituent. Liquid products and carbon also are formed. At still higher temperatures, up to 900°, aromatic hydrocarbons are formed. Thus at these high temperatures the changes that this relatively simple hydrocarbon undergoes are quite complex.

In the pyrolysis of *n*-butane the initial reactions have been identified by passing the hydrocarbon rapidly through a heated zone, before the secondary reactions take place to any considerable extent. Decomposition begins at a temperature of 365°. The main products are methane and propylene; minor products, ethane, ethylene, and hydrogen. At higher temperatures other reactions may take place, as the data of Table 21 show.

The respective products are: (1) methane and propylene, (2) ethane and ethylene; (3) hydrogen and butenes; (4) hydrogen and butadiene. The reactions would be endothermic if they could take place at the ordinary temperature, as shown by the ΔH values. Those obtained from heats of combustion data are more accurate.

Important conclusions can be drawn from the table. These endothermic reactions, like the pyrolysis of methane and ethane, take place only at high temperatures. It should be noted moreover that butane decomposes more easily than methane or ethane. Energy must be supplied for the breaking of stable bonds, since the bond energies are: C—C bond, 58.6 kcal.; C—H

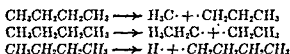
nd, 87.3 kcal. The reactions that require the absorption of the greatest nount of energy take place the least readily. However, with rise in temrature the dehydrogenation reactions become more important, from the inciple of Le Chatelier (p. 43).

ABLE 21 **Dehydrogenation and Pyrolysis of *n*-Butane**

ACTION	PRODUCTS	ΔH CALCULATED FROM		PROPORTION OF BUTANE DECOMPOSED AT		
		bond energies kcal.	heats of combustion kcal	600°	650°	700°
1	$CH_4 + CH_3CH{=}CH_2$	+17	+16 8	48 5	48	44
2	$CH_3CH_3 + CH_2{=}CH_2$	+17	+22 1	34.5	37.7	46
3	$H_2 + C_4H_8$	+30	+30 0	16	12 3	5
4	$2H_2 + CH_2{=}CHCH{=}CH_2$	+57	+58 0			4

If the time of heating is extended other reactions take place, such as demposition and dehydrogenation of the first reaction products and polymeration to more complicated compounds, including cyclization to aromatic mpounds. At higher temperatures decomposition is more complete and e breakdown into smaller molecules is more extensive. Finally, at temratures where methane decomposes easily, hydrogen and carbon are the ain products.

Considerable evidence indicates that in these high temperature reactions ee radicals are formed by the scission of bonds.



$$CH_3CH_2CH_2CH_3 \longrightarrow H_3C\cdot + \cdot CH_2CH_2CH_3$$
$$CH_3CH_2CH_2CH_3 \longrightarrow H_3CH_2C\cdot + \cdot CH_2CH_3$$
$$CH_3CH_2CH_2CH_3 \longrightarrow H\cdot + \cdot CH_2CH_2CH_2CH_3$$

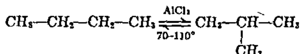
he mechanism by which the final products result is rather complicated and eed not be discussed here.

Higher hydrocarbons at elevated temperatures undergo decomposition and ehydrogenation more readily than butane. It is not feasible to write a rection illustrating the decomposition of a higher paraffin hydrocarbon because the much greater complexity of the system, compared to *n*-butane. The ature of the products, *i.e.*, whether due mainly to decomposition, dehydroenation, polymerization, or cyclization, depends upon the temperature, time heating, pressure, and catalyst. The main object of cracking in the past as been the production of liquid hydrocarbons in the boiling range of gasone, and also to produce "unsaturates" possessing valuable antiknock proprties.

The increasing use of gaseous olefins in the production of synthetic gasoline nd of butadiene for synthetic rubber has changed the object of cracking, so

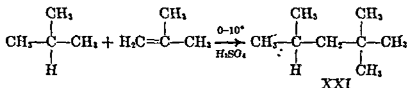
that instead of liquids being the only desired product, more emphasis is being placed upon the gases. The application of these is discussed in the next three chapters.

5. *Isomerization.* This is accomplished by heating a normal chain hydrocarbon under pressure with anhydrous aluminum chloride and hydrogen chloride. Ordinarily hydrocarbons are stable, but in contact with this powerful catalyst, normal hydrocarbons, *n*-butane and *n*-pentane, isomerize to the iso hydrocarbons. Other reactions may take place at the same time, resulting in the formation of both lower and higher alkanes. The reactions of isomerization are reversible.



Isobutane has become important industrially in the alkylation process of producing synthetic gasoline.

6. *Alkylation.* This is typified in the reaction of isobutane with isobutylene, $(CH_3)_2C{=}CH_2$.

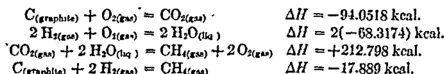


Sulfuric acid, 100 per cent, is a catalyst for this reaction. The product, 2,2,4-trimethylpentane, XXI, is a valuable fuel for the gasoline engine because of its high antiknock value. Hydrogen fluoride catalyzes the alkylation reaction and at temperatures below 0°.

7. *Cyclization.* At high temperatures where dehydrogenation is important, elimination of hydrogen may take place in such a way that a bond is formed between carbon atoms separated by four other carbon atoms. In this way a cyclic hydrocarbon may be formed. Usually these are aromatic hydrocarbons, benzene and toluene, mainly. An important industrial process was developed during World War I and improved during World War II for the production of toluene.

Thermochemistry of the Paraffins. The heats of combustion of hydrocarbons furnish important data, because from them can be calculated the heats of formation of the hydrocarbons from the elements, and the heat changes in many organic reactions. When the entropies of the compounds involved are known also, it is possible to obtain values for the free energies (refer to Chap. 2).

The heat of formation of methane can be calculated from ΔH of formation of carbon dioxide (ΔH of combustion of carbon), -94.0518 kcal., ΔH of formation of water (ΔH of combustion of hydrogen), -68.3174 kcal., and ΔH of combustion of methane, -212.798 kcal., per mole.



$$C_{(graphite)} + O_{2(gas)} = CO_{2(gas)} \qquad \Delta H = -94.0518 \text{ kcal.}$$
$$2\,H_{2(gas)} + O_{2(gas)} = 2\,H_2O_{(liq)} \qquad \Delta H = 2(-68.3174) \text{ kcal.}$$
$$CO_{2(gas)} + 2\,H_2O_{(liq)} = CH_{4(gas)} + 2\,O_{2(gas)} \qquad \Delta H = +212.798 \text{ kcal.}$$
$$C_{(graphite)} + 2\,H_{2(gas)} = CH_{4(gas)} \qquad \Delta H = -17.889 \text{ kcal.}$$

If one mole of methane at one atmosphere pressure could be formed at 25° from the elements, 17.889 kcal. would be liberated. The reaction would be exothermic. Thus it is possible to calculate ΔH for a reaction which does not take place at the ordinary temperature.

In Table 22 are listed the heats of combustion, ΔHc, and heats of formation, ΔHf of a number of alkanes, as determined by Rossini and co-workers at the

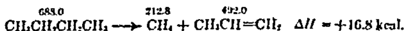
TABLE 22 **Heats of Combustion, ΔHc, and Heats of Formation, ΔHf, of Some Alkanes in the Gaseous State at 25° (in kcal. per mole [a])**

HYDROCARBON	ΔHc	DIFFERENCE	ΔHf	DIFFERENCE
Methane	−212.798		−17.889	
Ethane	−372.820	−160.022	−20.236	−2.347
Propane	−530.605	−157.785	−24.820	−4.584
n-Butane	−687.982	−157.377	−29.812	−4.992
n-Pentane	−845.16	−157.32	−35.00	−5.18
n-Hexane	−1002.57 [b]	−157.25	−39.96	−4.96
n-Heptane	−1160.01 [b]	−157.52	−44.89	−4.93
n-Octane	−1317.45 [b]	−157.39	−49.82	−4.92
n-Nonane	−1474.90 [b]	−157.53	−54.74	−4.92
n-Decane	−1632.34 [b]	−157.42	−59.67	−4.93
Isobutane	−686.342		−31.452	
Isopentane	−843.24		−36.92	
Neopentane	−840.49		−39.67	
Δ per CH_2		−157.44		−4.93

[a] Data from Circular C461, National Bureau of Standards, Washington, D. C., 1947.
[b] From ΔHc in the liquid state; *n*-hexane, −995.01; *n*-heptane, −1151.27; *n*-octane, −1307.53; *n*-nonane, −1463.80; *n*-decane, −1620.06 kcal.

United States Bureau of Standards (1945). The weighted average difference, Δ, in the heats of combustion of alkanes above *n*-pentane is −157.44 kcal., and in the corresponding heats of formation is −4.93 kcal. These are respectively the ΔH of combustion and of formation of methylene, CH_2. The small difference between the ΔHf values of methane and ethane, *viz.*, −2.3 kcal., means that methane is relatively more stable than ethane.

Heats of Reaction from Heats of Combustion. When heats of combustion are known accurately, heats of reaction may be calculated with a higher degree of accuracy than from bond energies. Using heat of combustion data from Tables 22 and 24, ΔH for the decomposition of *n*-butane to methane and propylene (reaction 1, Table 21) is +16.8 kcal.



$$\overset{688.0}{CH_3CH_2CH_2CH_3} \longrightarrow \overset{212.8}{CH_4} + \overset{492.0}{CH_3CH{=}CH_2} \qquad \Delta H = +16.8 \text{ kcal.}$$

The $-\Delta H$ of combustion of the products, 704.8 kcal., exceeds that of butane, 688.0 kcal., by 16.8 kcal. This means that the products have a higher energy content than butane. Therefore energy must be absorbed when they are formed from butane, and the amount that would be absorbed, if the reaction could take place at 25° would be 16.8 kcal., since the same number of moles of carbon dioxide and water result from reactant and products, on combustion. The reaction as written above is endothermic and ΔH is positive. In this reaction there is good agreement with ΔH calculated from bond energies, *viz.*, +17 kcal.

PROBLEMS

1. An alkane (name below) was mixed with an excess of air (the volume of the mixture is given under A), this was exploded (the volume of the dried gas is given under B), and then was allowed to stand over solid sodium hydroxide until the volume was constant (the final volume is given under C). Calculate the initial volume of the alkane, assuming all measurements made at the same temperature and pressure.

	Alkane	*A* cc	*B* cc	*C* cc.
a)	Methane	35.0	32.0	
b)	Ethane	50.0		41.0
c)	Propane	84.0	78.6	
d)	Butane	100.0		88.0

2. Show the theoretically possible number of structural isomers of the following by writing either the graphic or the condensed formulas.

a) CH_2FCl
b) CF_2Cl_2
c) CHF_2Cl
d) $C_2H_4Br_2$
e) C_2H_4FCl
f) $C_2H_3Cl_3$
g) $C_2H_3Cl_2Br$
h) $C_2H_2Cl_4$
i) $C_2HCl_2Br_3$
j) $C_2H_2Cl_2Br_2$
k) $C_3H_6F_2$
l) C_3H_6FCl
m) $C_3H_5Br_3$
n) $C_3H_5Br_2I$
o) $C_3H_5ClBr_2$

3. Name the compound in the question above.

4. Show how to calculate ΔH for the following reaction at room temperature. If a sufficiently powerful catalyst were available, do you think the reaction really would proceed to any considerable extent, as written?

a) $CO + 3\,H_2 \longrightarrow CH_4 + H_2O$
b) $CO_2 + 2\,H_2O \longrightarrow CH_4 + 2\,O_2$
c) $CH_3Cl + CH_4 \longrightarrow C_2H_6 + HCl$
d) $CH_2Cl_2 + CH_4 \longrightarrow C_2H_4 + 2\,HCl$
e) $C_2H_6 + F_2 \longrightarrow C_2H_5F + HF$
f) $CH_3Cl + HCl \longrightarrow CH_4 + Cl_2$
g) $C_2H_4 + H_2 \longrightarrow C_2H_6$
h) $C_2H_6 \longrightarrow C_2H_4 + H_2$
i) $C_3H_8 \longrightarrow C_2H_4 + CH_4$
j) $CH_4 + CH_4 \longrightarrow C_2H_6 + H_2$

5. Name the product or products you predict would result from the action of metallic sodium with:

a) CH_3CH_2I
b) $CH_3CH_2CH_2Br$
c) $(CH_3)_2CHI$
d) $CH_3I + CH_3(CH_2)_2CH_2I$
e) $CH_3CH(C_2H_5)CH_2I$
f) $CH_3CH_2CH_2CHBrCH_3$

6. Name the following in two ways: (1) by the I.U.C. system; (2) any other way.

a) $CH_3(CH_2)_4CH_3$
b) $CH_3CH(CH_3)CH(C_2H_5)_2$
c) $CH_3CH_2CH_2C(CH_3)_3$
d) $(CH_3)_2CHCH(CH_3)_2$
e) $CH_3CH(CH_3)CH(CH_3)C_2H_5$
f) $(CH_3)_2CH(CH_2)_3CH_3$
g) $CH_3CH(CH_3)(CH_2)_4CH_3$
h) $CH_3C(C_2H_5)_3$
i) $CH_3C(C_2H_5)_2(CH_2)_2CH_3$
j) $C(C_2H_5)_4$

7. Name the following by the I.U.C. system:

a) $(C_2H_5)_2CH(CH_2)_2CH_3$
b) $(CH_3)_3CCH(CH_3)CH(CH_3)_2$
c) $(CH_3)_2CHC(CH_3)_2CH(C_2H_5)_2$
d) $CH_3CH(CH_3)CH(CH_3)CH(CH_3)C_2H_5$
e) $(C_2H_5)_2CHCH(CH_3)_2$
f) $(CH_3)_2CHCHClCHClCH_3$
g) $CH_3CH_2CHClC(CH_3)_2CH(C_2H_5)CH_2Cl$
h) $CH_2Cl(CH_2)_2CH(CH_3)CH(CH_3)_2$
i) $CH_3CH(CH_2Br)CCl(CH_3)C(CH_3)_3$
j) $CH_2ClCH_2CHBrCH(C_2H_5)_2$

8. By means of equations show the possibilities of preparing *n*-pentane from monoiodo compounds by:

a) decomposition of a Grignard reagent
b) reduction by the zinc-copper couple
c) the Wurtz synthesis

9. Write a balanced equation with structural formulas for the following chemical change:

a) *n*-butane by the action of water on a Grignard reagent
b) *n*-pentane from an iodine compound
c) *n*-hexane by the Wurtz synthesis
d) *n*-octane by the Wurtz synthesis
e) isopentane by decomposition of a Grignard reagent
f) isopentane from an iodine compound
g) ethyl chloride from an alkane
h) ethyl bromide from an alkane
i) 2-chloropropane from an alkane
j) 2-chlorobutane from an alkane
k) nitromethane from an alkane
l) 1-nitropropane from an alkane
m) 2-nitrobutane from an alkane
n) *n*-heptane by the Kolbe synthesis
o) 2-chloro-2-methylpropane from an alkane
p) 2-nitro-2-methylpropane from an alkane

10. Which alkane has a molecular weight corresponding to the first number, and has just the number of structurally isomeric derivatives indicated.

a) 86; 2 monobromo
b) 100; 4 monobromo
c) <85; 4 monobromo
d) >44; 1 monobromo
e) 100; 3 monobromo
f) 86; 4 monobromo
g) 86; 3 monobromo
h) >100; 1 monobromo
i) 72, 10 dibromo
j) 86; 12 dibromo
k) 86; 2 monobromo and 6 dibromo
l) 100; 3 monobromo and 10 dibromo

11. Show the calculations involved in obtaining for the following the heat of formation from the elements:

a) ethane b) *n*-propane c) *n*-butane

CHAPTER 5

Alkenes, Olefins, the Ethylene Series, C_nH_{2n}

Complex mixtures of hydrocarbons are obtained when petroleum or petroleum fractions undergo pyrolysis during cracking (p. 55). These mixtures are composed mainly of saturated and unsaturated hydrocarbons. The unsaturated hydrocarbons are largely olefins, *i.e.*, acyclic (open-chain) hydrocarbons whose formulas conform to the general formula, C_nH_{2n}. The simplest member of the series, ethylene, originally was called olefiant gas (L. *oleum*, oil + *facio*, make), because it is converted into an oil, *viz.*, ethylene chloride, by the action of chlorine gas.

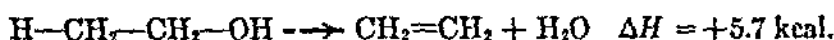
The members of the olefin (alkene) series of hydrocarbons resemble the paraffin hydrocarbons in having an acyclic (open-chain) structure, and differ in having two hydrogen atoms less than the paraffin hydrocarbons of the corresponding number of carbon atoms. The simplest member of the series should be methylene, CH_2. No compound of this formula has ever been prepared. Instead the usual product is ethylene, C_2H_4. However, methylene molecules can be detected in some gaseous reaction products at low pressures.

Ethylene, ethene, C_2H_4. This is the first member of the olefin series. Ethylene is a colorless gas having a characteristic sweetish odor. It is slightly soluble in water, more soluble in alcohol or in ether, about two volumes to one of solvent. Its critical temperature is 13° and its critical pressure exceeds 50 atmospheres. The explosive limits with air are 4 to 22 per cent. It burns with a luminous flame.

Preparation of Ethylene. Ethylene is produced in large quantities in the petroleum industry as the result of cracking of various hydrocarbon products. It usually is mixed with other gases, *e.g.*, hydrogen, alkanes, and other alkenes, from which it can be separated reasonably well by the distillation methods employed in the petroleum industry. Other methods are available for preparing ethylene, as described below. Of these (2) and (3) are the most convenient for the laboratory preparation of relatively small amounts, and (3) for obtaining pure ethylene.

1. *Catalytic gas phase decomposition of ethyl alcohol.* At 350 to 400° ethyl alcohol undergoes partial decomposition to ethylene and water when in contact with certain catalysts, *i.e.*, aluminum oxide, thorium oxide, or anhydrous

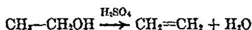
aluminum sulfate. The gas phase reaction, if it could be carried out at 25°, would be endothermic, according to bond energy values.



$$H—CH_2—CH_2—OH \longrightarrow CH_2{=}CH_2 + H_2O \quad \Delta H = +5.7 \text{ kcal.}$$

Alcohol vapor is passed through a hot tube containing the catalyst. The exit gas is cooled and any unchanged alcohol is removed by condensation and scrubbing with water. The alcohol can be purified and recirculated. During World War I large quantities of ethylene were produced this way as one step in the manufacture of mustard gas. The reaction is discussed in more detail in Chapter 10, Alcohols.

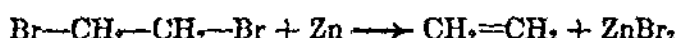
2. *Dehydration of ethyl alcohol by heating with concentrated sulfuric acid.* At temperatures of 150 to 160°, ethylene is evolved.



$$CH_3—CH_2OH \xrightarrow{H_2SO_4} CH_2{=}CH_2 + H_2O$$

The reaction is discussed in more detail under Alcohols, Chapter 10.

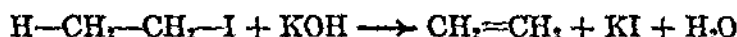
3. *Elimination of two bromine atoms from a molecule of ethylene bromide (1,2-dibromoethane).* This takes place readily when the bromide in alcoholic solution is heated with metallic zinc. The method is of value in the preparation of pure ethylene, for ethylene bromide can be obtained pure by distillation and crystallization.



$$Br—CH_2—CH_2—Br + Zn \longrightarrow CH_2{=}CH_2 + ZnBr_2$$

This operation sometimes is called **debromination.** It is one example of **dehalogenation,** *i.e.*, the removal of halogen from an organic molecule.

4. *Elimination of a molecule of a hydrogen halide from an ethyl halide.* When ethyl iodide, C_2H_5I, is dropped onto hot potassium hydroxide, the strong base extracts a molecule of hydrogen iodide.



$$H—CH_2—CH_2—I + KOH \longrightarrow CH_2{=}CH_2 + KI + H_2O$$

A modification which consists in passing the vapor through a hot zone containing the base, can be applied to ethyl bromide and ethyl chloride. This operation sometimes is called **dehydrohalogenation.**

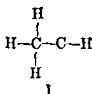
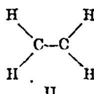
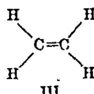
5. *Hydrogenation of acetylene.* Acetylene, C_2H_2, absorbs hydrogen in the presence of a hydrogenating catalyst. By controlling conditions properly the reaction can be stopped as soon as one mole of hydrogen has been absorbed.



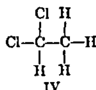
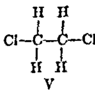
$$H_2 + C_2H_2 \longrightarrow C_2H_4 \quad \Delta H = -42 \text{ kcal.}$$

Suitable catalysts are finely divided palladium and platinum at room temperature and Raney nickel at somewhat elevated temperatures (100° or higher).

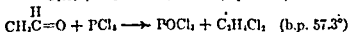
Structure of Ethylene. The selection of a structure for ethylene which is compatible with its chemical behavior is a good illustration of the way organic chemists decide questions of structure. *On the basis of a valence of one for* hydrogen, three different formulas can be written, I, II, and III. In I, one carbon atom is tetravalent, the other bivalent; in II, both are trivalent; in III, both are tetravalent.

Formula I is eliminated as a result of the structure of the compound formed by the reaction between ethylene and chlorine to form ethylene chloride, $C_2H_4Cl_2$, a dichloroethane. There are two dichloroethanes, 1,1-dichloroethane, IV, and 1,2-dichloroethane, V.

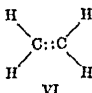
One, b.p. 83.7°, is obtained from ethylene and chlorine, the other, b.p. 57.3°, from acetaldehyde, CH_3—CHO, by the action of phosphorus pentachloride.

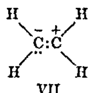
This second reaction involves an exchange of two atoms of chlorine for one of oxygen. The product therefore has structure IV, since both chlorine atoms are attached to the same carbon atom. Ethylene therefore cannot be I, for this would give IV with chlorine.

Decision between II and III was early made on the basis that compounds were unknown in which a single trivalent carbon atom was present. So if compounds are unstable because of the presence of one trivalent carbon atom, ethylene would not be expected to be stable if it contained two trivalent carbon atoms. Later, in 1900, triphenylmethyl, $(C_6H_5)_3C$, was discovered. This contains a trivalent carbon atom. However it exists only in solution and is very much more reactive than ethylene, rapidly reacting with iodine and with oxygen, whereas ethylene reacts only slowly. The carbon atoms of ethylene therefore are not in the highly reactive state characteristic of trivalent carbon. Thus II is not acceptable as the structure of ethylene. Historically, therefore, ethylene correctly came to be represented by formula III. The three-dimensional structures are shown in Figure 3, page 15.

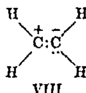
In formula III, the two carbon atoms are represented as being joined to each other by two valence bonds, a double bond. The electronic structure is shown by VI. The molecule is symmetrical, as shown by the value of the dipole moment, which is zero. The carbon-to-carbon separation is 1.34 Å, considerably less than the single bond distance of 1.54 Å in ethane. The shorter distance can be ascribed to the greater attractive force operating between four electrons and the two positive atomic centers which they join, whereas in ethane only two electrons hold the carbon atoms together.



VI



VII



VIII

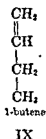
Within recent years the structure of ethylene has been modified to include resonance forms also. It is now believed that the structure is a resonance hybrid involving also VII and VIII, in addition to VI. Each of the last two makes only a small contribution to the overall structure, due to its much lower stability. However, the two are believed to be important in connection with chemical reactivity. Ethylene is said to be **unsaturated,** in contrast to ethane, which is **saturated.**

Reactions of Ethylene. Ethylene undergoes the general reactions of alkenes described later. Usually ethylene reacts more slowly than other olefins.

Uses of Ethylene. Ethylene produces a very hot flame with oxygen and sometimes is used in welding. In low concentration it hastens the ripening of some fruits and has been used for ripening citrus fruits. It has valuable anesthetic properties with less undesirable aftereffects than ether or chloroform. Ethylene can serve as a source of ethyl alcohol by the process of absorption in sulfuric acid and hydrolysis of the resulting monoethyl sulfate. From ethylene are manufactured many organic substances, among them ethylene glycol and related compounds (solvents), styrene, an intermediate in the manufacture of "synthetic" rubber (Chap. 6), and vinyl chloride, an intermediate in the manufacture of certain plastics (Chap. 8).

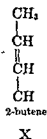
Propylene, Propene, C_3H_6. This usually is a constituent of the gases produced in the cracking process. It may be prepared by reactions similar to those described for ethylene. It is absorbed readily at room temperature by sulfuric acid as dilute as 80 per cent, which brings about hydration to isopropyl alcohol. *This is an industrial process. Polymerization takes place* when propylene is absorbed by concentrated sulfuric acid. Propylene reacts rapidly with liquid bromine.

Butylene, Butene, C_4H_8. There are four butenes known (Table 23, p. 65), although only three would be predicted on the basis of structure alone, *viz.*, two related to *n*-butane, IX and X, and one related to isobutane, XI. Actually, three are related to *n*-butane, *viz.*, IX, XII, and XIII.



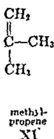
1-butene

IX



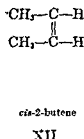
2-butene

X



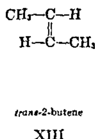
methyl-propene

XI



cis-2-butene

XII



trans-2-butene

XIII

The four compounds illustrate three types of isomerism. The isomerism of IX and X is due merely to a difference in the position of the double bond and thus is position isomerism (see Isomerism, Chap. 4). The isomerism of IX and XI is chain isomerism, like that of *n*-butane and isobutane. The isomerism of XII and XIII is due to a different spatial arrangement of the atoms in the molecule. It is called **stereoisomerism.** Other types of stereoisomerism are known. This type of stereoisomerism is called **geometrical isomerism** or *cis,trans*-isomerism.

Geometrical Isomerism. When each of the two unsaturated carbon atoms in an organic molecule is attached to two different univalent atoms or radicals, two different arrangements of the groups in space are possible, as shown in Figure 7.

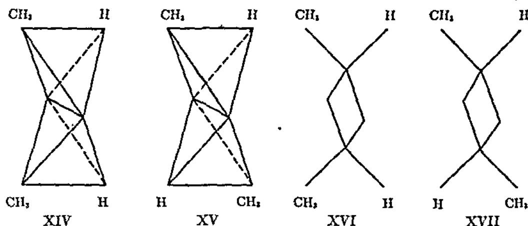


Figure 7 · Space Formulas of the Isomeric 2-Butenes

Since the tetrahedra are joined at two corners, they are not free to rotate; consequently the two structures XIV and XV (or XVI and XVII) cannot be superposed, and actually represent two different substances. It is more convenient to represent them by means of the projection formulas, XII and XIII, page 63. The isomer in which similar radicals lie on the same side of the double bond is called the *cis*-, and on opposite sides, the *trans*-isomer (L. *cis*, on the side of; *trans*, across from). A limitation on the use of projection formulas is the fact that they cannot be removed from the plane of the paper.

The above explanation of *cis,trans*-isomerism is based on the classical concept of the ethylenic double bond. This is still a satisfactory picture for this purpose but it does not explain the extraordinary chemical reactivity of this bond (p. 68), in comparison to that of a single bond.

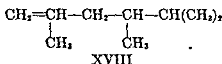
Nomenclature. Alkenes may be named in more than one way, as shown in Table 23. The classical method has been to change the ending -ane of the paraffin series to -ylene and to indicate the position of the double bond by Greek letters. In the I.U.C. system the ending -ane is changed to -ene and the longest chain containing the double bond is selected and numbered so as to give the double bond the smaller number. Some chemists use this number as a prefix, others as a suffix. Substituents are then named and

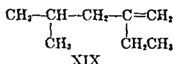
numbered as in the case of paraffin hydrocarbons. Alkenes, when not too complicated in structure may be named also as derivatives of ethylene. The

TABLE 23 | Names and Properties of the Butenes

NAMES			FORMULA	B.P. °C	F.P. °C
common	I.U.C.	derivative of ethylene			
α-Butylene	1-Butene	Ethylethylene	$CH_2{=}CHCH_2CH_3$	−6.5	<−195
β-Butylene	2-Butene	Symmetrical dimethylethylene			
cis-	*cis-*	*cis-*	$CH_3{-}CH{=}CH{-}CH_3$ (cis)	+3.73	−139.3
trans-	*trans-*	*trans-*	$CH_3{-}CH{=}HC{-}CH_3$ (trans)	+0.96	−105.8
Isobutylene	2-Methylpropene	Unsymmetrical dimethylethylene	$CH_3{-}C(CH_3){=}CH_2$	−6.6	−140.7

I.U.C. method is illustrated in the case of XVIII and XIX which are respectively 2,4,5-trimethyl-1-hexene and 2-ethyl-4-methyl-1-pentene (or 4-methyl-2-ethyl-1-pentene).





Higher Alkenes. The number of isomeric alkenes is greater than that of the corresponding alkanes because of the double bond, which may be in different positions in the molecule and which, in addition, may give rise to *cis,trans*-isomers. In Table 24 are listed the first nine members of the homologous series of 1-alkenes (α-olefins), some isomeric alkenes, and some of their physical constants. Alkenes resemble alkanes as regards solubility in organic solvents and insolubility in water.

General Methods of Preparation. Individual alkenes may be prepared by methods which in general resemble those for ethylene. The first three methods when used for hydrocarbons above propylene often yield mixtures.

1. *Dehydrohalogenation of an alkyl halide,* $C_nH_{2n+1}X$. Hot potassium hydroxide removes from an alkyl halide the elements of hydrogen halide.

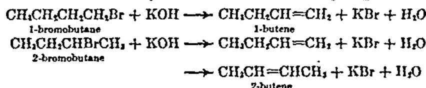


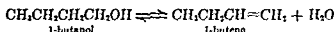
TABLE 24 | Constants of Some Alkenes

NAME		FORMULA	M.P. °C	B.P. °C	D_4^{20}	n_D^{20}	ΔH OF		
I.U.C.	trivial						combustion [b,c] kcal./mole	formation [b,c] kcal./mole	hydrogenation [b] kcal./mole
			THE LOWER 1-ALKENES [a]						
Ethene	Ethylene	$CH_2{=}CH_2$	−169.4	−102 4			−337.23	+12.50	−32.732 [d]
Propene	Propylene	$CH_2{=}CHCH_3$	−185	−47 7			−491 99	+4 88	−29.699 [d]
1-Butene	α-Butylene	$CH_2{=}CHCH_2CH_3$	< −190	−6.5	0 6170 [e]		−649 76	+0 28	−30 092 [d]
1-Pentene	α-Amylene	$CH_2{=}CH(CH_2)_2CH_3$		30.1	.6429	1 3714	−806.85	−5 00	−30 0
1-Hexene	α-Hexylene	$CH_2{=}CH(CH_2)_3CH_3$	−138	63 5	.6747	1 3886	−964.26	−9 96	−30 0
1-Heptene	α-Heptylene	$CH_2{=}CH(CH_2)_4CH_3$	−119.1	93.1	.6976	1 3999	−1121.69	−14.89	−30 0
1-Octene	α-Octylene	$CH_2{=}CH(CH_2)_5CH_3$	−104	122.5	7159	1 4103	−1279.13	−19.82	−30 0
1-Nonene	α-Nonylene	$CH_2{=}CH(CH_2)_6CH_3$		146	.7308	1 4161	−1436 58	−24.74	−30.0
1-Decene	α-Decylene	$CH_2{=}CH(CH_2)_7CH_3$		171	.743	1.4217	−1594 02	−29.67	−30.0
			OTHER ALKENES						
cis-2-Butene	*cis*-β-Butylene	$\frac{CH_3}{H}{>}C{=}C{<}\frac{CH_3}{H}$	−139.3	3.73			−648.11	−1 36	−28.450 [d]
trans-2-Butene	*trans*-β-Butylene	$\frac{CH_3}{H}{>}C{=}C{<}\frac{H}{CH_3}$	−105 8	0.3			−647.07	−2 40	−27.407 [d]
Methylpropene	Isobutylene	$CH_2{=}C(CH_3)_2$	−140.7	−6 6	0.6190 [f]		−646.13	−3.31	−28.109 [d]
cis-2-Pentene	*cis*-β-Amylene	$\frac{CH_3}{H}{>}C{=}C{<}\frac{CH_2CH_3}{H}$	−151.4	36 7	6554	1.3828	−805.3	−6 71	−28,49
trans-2-Pentene	*trans*-β-Amylene	$\frac{CH_3}{H}{>}C{=}C{<}\frac{H}{CH_2CH_3}$		36.1	6475	1.3798	−804.3	−7.59	−27.41
2-Methyl-2-butene	Trimethylethylene	$CH_3CH{=}C(CH_3)_2$	−123	38 6	6596	1 3876	−801.7	−10.17	−26.745 [d]
2,3 Dimethyl-2-butene	Tetramethylethylene	$(CH_3)_2C{=}C(CH_3)_2$	−74.2	73.4	.7054	1.4116	−958 3	−15.9	−26.576 [d]

[a] Data other than thermodynamic from *Physical Constants of Hydrocarbons*, Vol. I, by G. Egloff, Reinhold Publishing Corp., New York, 1939.
[b] At 25° in the gaseous state. [c] Data from Circular C461, National Bureau of Standards, Washington, D. C., 1947.
[d] Calculated for 25° from experimental values at 82° (Kistiakowsky, *et al.*). [e] At −0.5°. [f] At 0 1°.

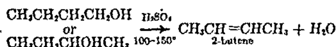
The relative order of reactivity is: iodides > bromides > chlorides. When a bromine atom is attached to a terminal carbon atom, usually the product is a 1-alkene, for the hydrogen atom comes from the adjacent carbon atom. When the bromine atom is attached to a secondary carbon atom, usually the product is a mixture; the results with 1-bromobutane and 2-bromobutane, above, are typical.

2. *Pyrolysis of an alcohol,* $C_nH_{2n+1}OH$. When the vapor of an alcohol is passed over a suitable solid, for example, aluminum oxide, thorium oxide, anhydrous aluminum sulfate, or other **dehydration catalyst**, at a temperature of 300 to 400°, an equilibrium is set up between alcohol, alkene, and water (see Chap. 10).



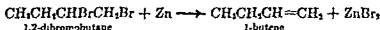
However, in the case of higher alcohols, the reaction is not this simple; thus some 2-butene also may be formed from 1-butanol. The amount of this is negligible with aluminum oxide as the catalyst when it contains some sodium carbonate.

3. *Dehydration of an alcohol,* $C_nH_{2n+1}OH$. When an alcohol is heated with sulfuric acid of the proper water content, an olefin is formed by the loss of a molecule of water.



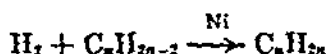
Concentrated sulfuric acid is not satisfactory with alcohols of three or more carbon atoms because it promotes polymerization of the olefin. Both the forward and reverse reactions are acid catalyzed (see Chap. 10). When its concentration is sufficiently high, the olefin escapes from solution. Under *acid conditions the sole product from the alcohols above is 2-butene* with none of the expected 1-butene. This shows that isomerization may be marked under acidic conditions.

4. *Debromination of an olefin dibromide,* $C_nH_{2n}Br_2$. When one of these, in which the bromine atoms are attached to adjacent carbon atoms, is heated with metallic zinc, the two bromine atoms are removed, with formation of a double bond.

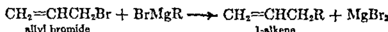


The reaction is useful for the preparation of pure olefins from purified dibromides.

5. *Reduction of an alkyne,* C_nH_{2n-2}. This may be accomplished by a reaction with sodium in liquid ammonia or by controlled hydrogenation in the presence of a suitable hydrogenation catalyst, *viz.,* nickel or palladium (see Chap. 6).



6 *Grignard synthesis* (see Chap. 9). Allyl bromide reacts with alkyl magnesium halides. The products are 1-alkenes (α-olefins).



$$\underset{\text{allyl bromide}}{CH_2{=}CHCH_2Br} + BrMgR \longrightarrow \underset{\text{1-alkene}}{CH_2{=}CHCH_2R} + MgBr_2$$

This is an excellent method of synthesis. Derivatives of allyl bromide, however, usually give rise to mixtures.

7. *From bromoethers.* This valuable method is described under ethers (Chap. 15)

Reactions of Alkenes. There are two types of reactions, *viz.*, substitution and addition Substitution is relatively less important.

Alkenes react spontaneously and rapidly with some reagents, for example, chlorine, bromine, hypochlorous acid, and aqueous potassium permanganate. They react slowly with many others, especially acids. In some cases, as with water, a catalyst is necessary. In general, ethylene reacts more slowly than the lower homologs, and a "tertiary base" olefin, for example, isobutylene or one of its homologs, reacts more rapidly than a normal olefin.

Reactions in which the ethylenic double bond is converted into a single bond are exothermic. In Table 25 are shown the ΔH values for a number of

TABLE 25 **Heat Changes in Additions to 1-Alkenes**[a]

REACTANT	PRODUCT	ΔH
H_2	RCH_2CH_3	−29 8
H_2O	$RCH(OH)CH_3$	−5 7
Cl_2	$RCHClCH_2Cl$	−33 8
Br_2	$RCHBrCH_2Br$	−20 5
I_2	$RCHICH_2I$	−13 4
HCl	$RCHClCH_3$	−9 7
HBr	$RCHBrCH_3$	−12.6
HI	$RCHICH_3$	−20.0
$RCH{=}CH_2$	$R(C_4H_6)R$	−17.2

[a] For gaseous reactions, from bond energies

reactions in the gaseous state, as calculated with bond energies. In general, a system consisting of an alkene and one of these reagents is less stable than the saturated compound. Therefore if the rate of reaction is finite, the saturated compound will be the final state of the system. Reversibility would be expected to be easiest where $-\Delta H$ is the smallest, *i.e.*, in the reaction with water. Actually, alcohols decompose more easily than any of the other products. To obtain ΔH for liquid systems the heats of vaporization must be taken into account.

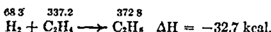
The rapid rates of many of the addition reactions of alkenes are related to the availability of electrons of the double bond. It is not evident from the

classical valence structures of Figure 7 that electrons of a double bond are more available than those of a single bond. However, in terms of quantum mechanical concepts, the ethylenic bond is made up of a *sigma*-bond (similar to the single bond of ethane) and a *pi*-bond. The electrons of the *pi*-bond are under less restraints than those of the *sigma*-bond, and are more easily displaced under the influence of an electric field or of a polar reagent. This accounts for an alkene having a higher dielectric constant than the corresponding alkane because of its greater polarizability, and for the ease with which the alkene reacts with an **electrophilic reagent** such as chlorine or bromine. An electrophilic reagent is one that seeks electrons. The strongest electrophilic reagents are good oxidizing agents, for example, chlorine, bromine, and nitric acid.

1. *Addition of hydrogen; hydrogenation.* Olefins add hydrogen in the presence of hydrogenating catalysts, *i.e.*, certain finely divided metals, such as nickel, palladium, and platinum (platinum oxide). Platinum and palladium are effective at room temperature. Raney nickel sometimes requires a higher temperature, about 100°; other forms still higher. These metals are easily poisoned by traces of sulfur compounds. Copper chromite is less sensitive to poisoning. It requires still higher temperatures, above 200°. Hydrogenations at high pressures, 100 to 500 atmospheres, may proceed without catalysis. Iron catalysts are used industrially.

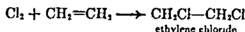
Heat changes in hydrogenation in the gas phase at 82° have been measured quite accurately. The values shown in Table 24 have been calculated to 25° C. It is interesting to note that $-\Delta H$ of hydrogenation decreases as methyl radicals replace hydrogen atoms on the unsaturated carbon atoms. Thus $-\Delta H$ of hydrogenation of tetramethylethylene is 26 58 kcal., while that of ethylene is 32.73 kcal. The $-\Delta H$ value from bond energies, *viz.*, 29.8 kcal., is a mean value. This corresponds most closely to 1-alkenes, $RCH{=}CH_2$.

Heats of hydrogenation can be calculated from the heats of combustion of hydrogen and of the two hydrocarbons involved, as in the reaction below, where the heats of combustion in kcal. per mole are written above the formulas.

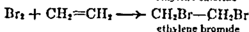


$$\overset{68.3}{H_2} + \overset{337.2}{C_2H_4} \longrightarrow \overset{372.8}{C_2H_6} \quad \Delta H = -32.7 \text{ kcal.}$$

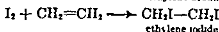
2. *Addition of halogens.* In the liquid phase chlorine and bromine usually react rapidly and quantitatively, iodine slowly and incompletely (see Table 25). However, ethylene reacts only slowly with liquid bromine. The reactions with ethylene are typical



$$Cl_2 + CH_2{=}CH_2 \longrightarrow \underset{\text{ethylene chloride}}{CH_2Cl{-}CH_2Cl}$$



$$Br_2 + CH_2{=}CH_2 \longrightarrow \underset{\text{ethylene bromide}}{CH_2Br{-}CH_2Br}$$



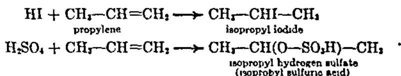
$$I_2 + CH_2{=}CH_2 \longrightarrow \underset{\text{ethylene iodide}}{CH_2I{-}CH_2I}$$

A mixture of chlorine and ethylene may explode if illuminated, for light hastens the reaction. Ethylene iodide may be obtained by passing ethylene into

a solution of iodine in alcohol. The product, a solid, is only slightly soluble. Ethylene iodide and other olefin iodides are unstable; they dissociate into iodine and the olefin. The chlorides and bromides are stable.

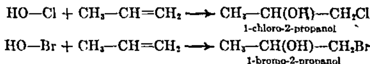
Unsaturation can be determined quantitatively with bromine, or with a reagent which supplies bromine, for example, bromine water, bromine in carbon tetrachloride, Hanus solution (bromine and iodine in glacial acetic acid), or aqueous potassium bromide, potassium bromate, and sulfuric acid. An excess of bromine is added to the material to be analyzed and after the reaction is over, the amount of unreacted bromine is determined.

3. *Addition of acids.* Strong acids add to the double bond of olefins. The hydrohalic acids react in concentrated aqueous solution or in some organic solvent, for example, acetic acid. The relative rates are in the order HI > HBr > HCl. Sulfuric acid reacts in the concentrated form or in slightly dilute form, for example, 80 per cent acid.



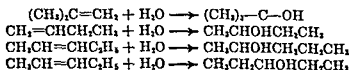
Also polymerization takes place in concentrated sulfuric acid and hydration in the diluted acid. The relative rates of absorption into 80 per cent sulfuric acid at 25° are. isobutylene, 158; 2-butene, 2.6; 1-butene, 1; propene, 1; ethylene, 0.003.

4. *Addition of hypohalous acids.* Hypochlorous and hypobromous acids add rapidly, even in dilute aqueous solution.



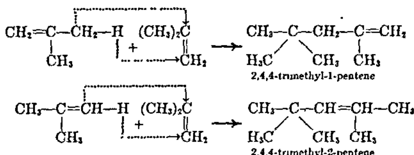
The products are halogenated alcohols. The rapidity of reaction seems to be due to the fact that the hypohalous acids are strong oxidizing agents.

5. *Addition of water; hydration.* This is the reverse of the reaction by which olefins are prepared (see Alcohols). A strong acid catalyst is necessary. Some olefins hydrate more easily than others, for example, isobutylene in dilute (1 *N*) aqueous acid hydrates directly to tertiary butyl alcohol, $(CH_3)_3COH$. The normal butenes and pentenes hydrate in 80 per cent sulfuric acid at room temperature. In this solution, addition of sulfuric acid also takes place, as described under (3) above. Ethylene does not hydrate under these conditions, but does hydrate slightly at 150° in contact with 70 per cent sulfuric acid.



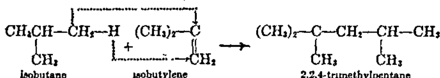
The hydroxyl group in the product is attached to a tertiary carbon atom if the olefin contained an unsaturated tertiary carbon atom, otherwise (except in the case of ethylene) to a secondary carbon atom.

6. *Addition of hydrocarbons: a) Polymerization.* In the presence of catalysts, olefins polymerize to dimers, trimers, and higher polymers. The reaction has become important industrially for the production of synthetic gasoline, synthetic oils, and some forms of "synthetic" rubber (see Chap. 6). Very active catalysts effective at room temperature and below, are boron trifluoride, anhydrous aluminum chloride, and some types of siliceous earths; less active are sulfuric acid and phosphoric acid. Isobutylene polymerizes easily, normal alkenes less easily, ethylene least easily. The dimer obtained from isobutylene by the action of sulfuric acid is called diisobutylene. It is a mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene.



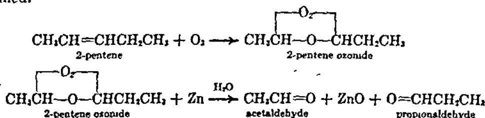
When hydrogenated, both of these are converted to 2,2,4-trimethylpentane, the "isooctane" of commerce. This is an important constituent of aviation gasoline (Chap. 7). Polymerization may continue, with formation of triisobutylene and higher polymers.

b) Alkylation. Alkanes may react in the presence of 100 per cent sulfuric acid or of anhydrous hydrogen fluoride, an especially effective catalyst.



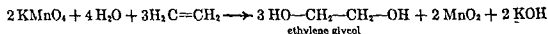
This is an important industrial reaction for it leads to the formation of highly branched alkanes of excellent antiknock properties (Chap. 7).

7. *Ozonolysis.* This involves the formation of an unstable ozonide by the action of ozone and the decomposition of this when water is added. The molecule is cleaved at the position of the double bond into acids and aldehydes of lower carbon content. In the presence of zinc, aldehydes only are formed.



By ozonolysis the position of the double bond in the molecule can be ascertained, for the products, aldehydes, usually can be identified readily, owing to the numerous reactions they undergo (Chap. 17).

8. *Oxidation with aqueous permanganate; hydroxylation.* An immediate reaction takes place accompanied by precipitation of manganese dioxide. This is called the Baeyer test for unsaturation. The product is a glycol, a dihydroxy compound.



$$2\,KMnO_4 + 4\,H_2O + 3H_2C{=}CH_2 \longrightarrow 3\,\underset{\text{ethylene glycol}}{HO{-}CH_2{-}CH_2{-}OH} + 2\,MnO_2 + 2\,KOH$$

With an excess of permanganate and under alkaline conditions a glycol molecule is oxidatively cleaved between the hydroxyl groups and two molecules of acid are formed.

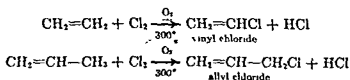


$$3[O] + R{-}CH(OH){-}CH(OH){-}R' \longrightarrow ROOCH + R'COOH + H_2O$$

The position of the double bond can be determined by identification of the resulting acids.

9. *Miscellaneous addition reactions.* Many other reagents add to olefins, as for example nitrogen trioxide, nitrogen tetroxide, nitrosyl chloride, sulfur chloride, sulfur dichloride, and mercuric salts. Olefins slowly undergo hydroxylation, *i.e.*, addition of two hydroxyl groups as in the Baeyer test, with hydrogen peroxide in the presence of osmium tetroxide, which acts catalytically. Industrially ethylene is converted to ethylene oxide by oxygen at about 275° in the presence of finely divided silver.

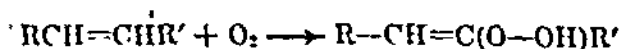
10. *Substitution.* When chlorine reacts with olefins in a liquid phase at room temperature, substitution as well as addition may take place. At elevated temperatures of 300° and higher, both types of reaction take place in the gas phase. In the presence of oxygen at these high temperatures, the addition reaction is suppressed. Ethylene and propylene yield respectively vinyl chloride and allyl chloride.



$$CH_2{=}CH_2 + Cl_2 \xrightarrow[300^\circ]{O_2} \underset{\text{vinyl chloride}}{CH_2{=}CHCl} + HCl$$

$$CH_2{=}CH{-}CH_3 + Cl_2 \xrightarrow[300^\circ]{O_2} \underset{\text{allyl chloride}}{CH_2{=}CH{-}CH_2Cl} + HCl$$

Oxygen is readily absorbed by a liquid olefin, with formation of a hydroperoxide:

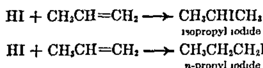


$$RCH{=}CHR' + O_2 \longrightarrow R{-}CH{=}C(O{-}OH)R'$$

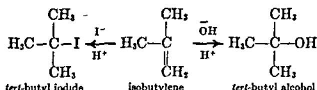
Such hydroperoxides are reactive and unstable. They liberate iodine from hydriodic acid, and thus interfere with the analysis of olefins by bromine absorption.

Unsymmetrical Addition. When an unsymmetrical reagent, *e.g.*, hy-

products are theoretically possible, depending upon which carbon atom accepts the iodine atom.

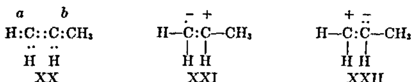


Actually the first reaction takes place to the almost complete exclusion of the second, for the sole product is isopropyl iodide. Likewise, sulfuric acid adds to form isopropyl sulfate. On hydration 1-butene is converted mainly to 2-hydroxybutane (2-butanol). Thus, the negative radical of the addendum becomes attached to the secondary carbon atom. Also, it joins a tertiary carbon atom in preference to a primary or secondary, if the molecule contains an unsaturated tertiary carbon atom, as in the reactions of isobutylene:



The relationships are generalized by Markownikoff's rule, which states that, in general, unsymmetrical addition to olefins produces largely that isomer in which the negative radical (Cl, Br, I, OH, SO_4H, etc.) is attached to the carbon atom to which the smaller number of hydrogen atoms is attached.

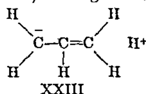
The course of the normal unsymmetrical addition reactions of propylene, other 1-alkenes, and isobutylene can be accounted for in terms of relative electronegativities of alkyl groups, as compared to hydrogen. The complete structure of propylene includes not only the stable, unexcited form, XX, but also the excited forms, XXI and XXII.



The first, XX, makes the main contribution to the structure. Since a hydrogen atom is more electronegative than a methyl radical (p. 38), electron pair *a* is more strongly attracted by H than pair *b* is by CH_3. Thus electrons are displaced towards the left, and XXI is more stable than XXII; the latter's contribution to the structure is insignificant. The course of the reaction is determined mainly by XXI. The negative radical of the addendum becomes attached to the more positive carbon atom of the olefin.

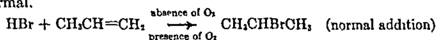
An extension of the resonance theory explains in still more detail why the carbon atom on the left, in XX, is negative. This invokes the concept of **hyperconjugation, or no-bond resonance.** In addition to XX, XXI, and XXII, another resonance form, XXIII, is regarded as possible.

In a C—H bond there is some ionic character, since carbon is more electronegative than hydrogen. The polarization of the bond can be indicated by C^-H^+. When this carbon atom, C-1, is saturated and is attached to an unsaturated carbon atom, C-2, the negative charge on C-1 can be trans-

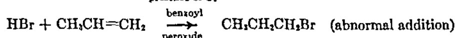


ferred to C-3 by resonance, leaving the positively charged hydrogen atom unbonded to carbon. Therefore C-3, the left-hand carbon atom in XXII, has a negative charge, and thus the positive part of the addendum attaches itself there.

There are exceptions to Markownikoff's rule, the most important of which are *those involving addition of hydrogen bromide. When the addition is* carried out in the absence of oxygen or of peroxides (organic or inorganic), the addition is normal. When peroxides are present, the addition may be abnormal.



$$HBr + CH_3CH{=}CH_2 \xrightarrow[\text{presence of } O_2]{\text{absence of } O_2} CH_3CHBrCH_3 \quad \text{(normal addition)}$$



$$HBr + CH_3CH{=}CH_2 \xrightarrow[\text{peroxide}]{\text{benzoyl}} CH_3CH_2CH_2Br \quad \text{(abnormal addition)}$$

In the presence of benzoyl peroxide, $(C_6H_5CO)_2O_2$, about 80 per cent of the product from propylene is 1-bromopropane (the abnormal product). Oxygen usually does not influence the course of the reaction of olefins, but many substituted olefins, as for example vinyl chloride, $CH_2{=}CHCl$, give abnormal addition products with hydrogen bromide in the presence of oxygen. The abnormal reaction is believed to be a chain reaction involving free radicals.

Uses of Alkenes. Alkenes are produced in large amounts in the petroleum industry. The lower alkenes are important for the production of: (1) secondary and tertiary alcohols, by hydration; (2) higher branched olefins, by polymerization; (3) higher branched alkanes, by alkylation; (4) dienes, by dehydrogenation.

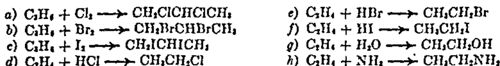
Identification of Alkenes. For distinguishing alkenes from alkanes, two reagents are used, *viz.*, aqueous permanganate or a dilute bromine solution, preferably one in carbon tetrachloride. Both are reduced rapidly with discharge of color. A dark precipitate is formed in the permanganate solution. Aqueous bromine also can be used, but this fails to differentiate between an alkene and a rapidly reacting alkane, for example, one containing a tertiary carbon atom, because hydrogen bromide, the other reaction product in the substitution reaction is not evolved, owing to its high solubility in water, whereas it is evolved when carbon tetrachloride is the solvent. The position of the double bond is determined by ozonolysis or by oxidation with an excess of alkaline permanganate. It is necessary to identify the reaction products in each case.

PROBLEMS

1. A measured volume, A, of a dry gas was mixed with a measured volume of dry air, B; after exploding and drying, the volume was C, and after standing over potassium hydroxide the volume decreased to D. What was the hydrocarbon?

	A cc.	B cc.	C cc	D cc.
a)	0.7	40.0	38.6	35.8
b)	0.8	30.0	28.8	26.1
c)	1.0	50.0	48.0	44.0
d)	1.2	50.0	47.6	44.0
e)	1.5	48.5	47.0	44.0
f)	1.8	70.0	67.3	61.9
g)	2.2	70.0	67.8	63.4

2. Using bond energies, calculate ΔH for the following reaction, disregarding heats of vaporization.



a) $C_3H_6 + Cl_2 \longrightarrow CH_2ClCHClCH_3$
b) $C_3H_6 + Br_2 \longrightarrow CH_2BrCHBrCH_3$
c) $C_3H_6 + I_2 \longrightarrow CH_2ICHICH_3$
d) $C_2H_4 + HCl \longrightarrow CH_3CH_2Cl$
e) $C_2H_4 + HBr \longrightarrow CH_3CH_2Br$
f) $C_2H_4 + HI \longrightarrow CH_3CH_2I$
g) $C_2H_4 + H_2O \longrightarrow CH_3CH_2OH$
h) $C_2H_4 + NH_3 \longrightarrow CH_3CH_2NH_2$

3. Write the structures and names of all of the theoretically possible olefins of the formula:

a) C_5H_{10}
b) C_6H_{12}, with a normal carbon chain
c) C_6H_{12}, with a branched carbon chain

4. Using only reactions studied in connection with the paraffin and olefin hydrocarbons, show by balanced equations the reactions you would employ for obtaining in the laboratory from 2-iodopropane, the following, reasonably free of any isomeric form:

a) propane
b) propene
c) 2-bromopropane
d) 1-bromopropane
e) 2-chloropropane
f) 2-hydroxypropane
g) *n*-hexane
h) 2,2-dimethylbutane
i) 1,2-dihydroxypropane
j) 1-chloro-2-hydroxypropane

5. Write balanced equations with structural formulas for the reactions you would employ for a practical laboratory preparation of the following, from a saturated compound of the same number of carbon atoms:

a) 2-butene
b) methylpropene
c) trimethylethylene
d) 2-pentene
e) 1-hexene
f) 2,4-dimethyl-2-pentene
g) 3-methyl-2-pentene
h) 1-heptene
i) 3-ethyl-2-pentene
j) 3-heptene
k) 1-octene
l) 4-*n*-propyl-3-heptene

6. Write the structure and give the name of the addition products formed from equal molal amounts of chlorine and the theoretically possible olefins of the formula:

a) C_5H_{10}, with a normal carbon chain
b) C_5H_{10}, with a branched carbon chain
c) C_6H_{12}, with a normal carbon chain
d) C_6H_{12}, with a branched carbon chain

7. Using heats of combustion, calculate ΔH of hydrogenation of:

a) propylene
b) 1-hexene
c) 1-butene
d) 1-pentene

8. Write the structural formula and the name of the compound formed between one mole of bromine and one mole of:

a) 1-butene
b) 2-butene
c) 2-pentene
d) 3-hexene
e) 3-heptene
f) 2-methyl-2-pentene
g) 2-methyl-1-pentene
h) 2,3-dimethyl-1-hexene
i) 3-ethyl-2-pentene
j) 3-methyl-3-hexene

9. Give the structure and name of the compound that you would expect to be the main product in the reaction of hydrogen iodide with:

a) *n*-propylethylene
b) trimethylethylene
c) symmetrical diethylethylene
d) symmetrical dimethylethylene
e) triethylethylene
f) unsymmetrical di-*n*-propylethylene
g) unsymmetrical methyl-*n*-propylethylene
h) unsymmetrical methylisopropylethylene
i) dimethylethylethylene
j) methyldiethylethylene

10. To a definite weight of hydrocarbon, A, dissolved in glacial acetic acid was added 25.0 ml. of aqueous bromide-bromate solution, 0.12 N in potassium bromide, $N/60$ in potassium bromate. Dilute sulfuric acid was added, the mixture was shaken in the dark potassium iodide was added, and the liberated iodine was back titrated with 0.05 N thio sulfate, using starch as indicator. The volume required was B. What was the hydr carbon?

a) $A = 0.0883$ g; $B = 8.0$ ml.
b) $A = 0.1222$ g; $B = 6.4$ ml
c) $A = 0.0934$ g; $B = 5.6$ ml.
d) $A = 0.1100$ g; $B = 5.2$ ml.
e) $A = 0.1021$ g; $B = 8.4$ ml.

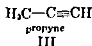
CHAPTER 6

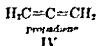
Alkynes, the Acetylene Series; Alkadienes, Diolefins, C_nH_{2n-2}

There are two types of hydrocarbons which are less saturated than the alkenes (olefins), *viz.*, the alkynes (alkines, acetylene hydrocarbons) and the alkadienes (diolefins). The molecule has two less hydrogen atoms than the corresponding alkene, and four less than the corresponding alkane. The alkyne contains one triple bond, the alkadiene, two double bonds. The formulas below show how propyne, III, and propadiene, IV, are related to propane, I, and propene, II.

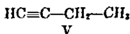


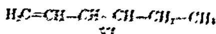






Nomenclature. In the I.U.C. system, the name of the acetylene hydrocarbon is obtained by changing the ending -ane of the paraffin hydrocarbon to -yne (or -ine), and that of the diolefin, to -adiene. In the case of higher members of the two series the longest chain containing the multiple (double or triple) bond or bonds is selected first, and the chain is numbered so as to indicate the position or positions in the chain by the lower of two possible numbers. The numbers may precede or follow, for example, V is 1-butyne or 1-butine (or butyne-1, etc.); VI is 1,3-hexadiene or hexadiene-1,3.





Substituents are indicated in the usual way.

ALKYNES

Acetylene, Ethyne, C_2H_2. This is the first member of the acetylene series of hydrocarbons and is the most important. It is a colorless gas [illegible] a pleasant ethereal odor when pure. However acetylene prepared from calcium carbide has a garlic-like odor owing to impurities, mainly [illegible] When liquefied, acetylene boils at $-84°$. It is slightly soluble in [illegible] solvents; one volume of water, benzene, or alcohol dissolves [illegible] volumes respectively of acetylene. One volume of acetone [illegible]

over the wide range of 3 to 82 per cent acetylene by volume are explosive when ignited.

Acetylene is important industrially. The very hot flame of the oxygen-acetylene torch is used for the cutting and welding of metals, especially steel. Also from acetylene many organic compounds are manufactured: (*a*) the chlorine addition products, acetylene dichloride and acetylene tetrachloride, much used as solvents; (*b*) acetaldehyde, from which other important chemicals, *e.g.*, acetic acid and acetone, can be manufactured; (*c*) unsaturated compounds such as vinyl chloride and vinyl acetate, the basis of an important group of synthetic resins and plastics; (*d*) vinyl acetylene, the basis of neoprene, a type of synthetic rubber.

Acetylene undergoes the reactions listed under general reactions of alkynes. The formation of metallic compounds should be discussed at this point, however, mainly because of the value of sodium acetylide in synthesis.

Acetylene as an Acid. *When acetylene is passed into a solution of sodamide* in anhydrous liquid ammonia, the monosodium salt, sodium acetylide, is formed.



$$NaNH_2 + C_2H_2 \longrightarrow C_2HNa + NH_3$$

The decomposition of sodamide by acetylene indicates that acetylene is a stronger acid than ammonia.

By the action of acetylene with ammoniacal silver or cuprous ion, gray insoluble silver acetylide or red cuprous acetylide is formed.



$$2\,Ag(NH_3)_2^+ + C_2H_2 \longrightarrow C_2Ag_2 + 2\,NH_3 + 2\,NH_4^+$$



$$2\,Cu(NH_3)_2^+ + C_2H_2 \longrightarrow C_2Cu_2 + 2\,NH_3 + 2\,NH_4^+$$

When dry these solids are liable to explode.

Under neutral or weakly acid conditions acetylene gives an insoluble precipitate with aqueous silver nitrate.



$$3\,AgNO_3 + C_2H_2 \longrightarrow AgNO_3 \cdot C_2Ag_2 + 2\,HNO_3$$

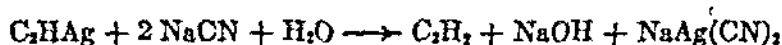
This reaction may be used for the quantitative determination of acetylene, by titration of the resulting nitric acid.

Metallic acetylides can be decomposed to yield acetylene. Sodium and calcium acetylides are decomposed by water alone.



$$C_2HNa + H_2O \longrightarrow C_2H_2 + NaOH$$

This indicates that water is a stronger acid than acetylene. The silver and cuprous salts are slowly decomposed by hydrochloric acid. They are decomposed more rapidly by aqueous sodium (or potassium) cyanide, due to the formation of the stable cyanide complex, as when silver cyanide or other insoluble silver salt dissolves in aqueous cyanide.



$$C_2HAg + 2\,NaCN + H_2O \longrightarrow C_2H_2 + NaOH + NaAg(CN)_2$$

Unsaturation enhances acidic properties. *Although a very weak acid,* acetylene is stronger than ethylene, which in turn is stronger than ethane.

umes at ordinary pressure and 300 volumes at a pressure of 12 atmospheres. In acetone solution acetylene is stable. On this account it is transported in cylinders, filled with a porous material, such as asbestos, and containing acetone.

Acetylene is formed directly from the elements, carbon and hydrogen, when these are heated in an electric arc. It is present also in the pyrolysis products of most hydrocarbons when the decomposition is carried out at a sufficiently high temperature, *i.e.*, above 1000° and up to 3000°. Acetylene has been identified in the decomposition products of ethane at 800°. At 1400° and during a short contact time, 50 per cent conversion to acetylene has been realized. Acetylene is present to about 0 1 per cent in coal gas and is formed in the incomplete combustion of many hydrocarbons as, for example, when the flame of a Bunsen burner strikes back.

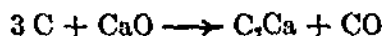
The formation of acetylene by the high temperature decomposition of numerous hydrocarbons is related to the fact that the thermodynamic stability of acetylene is increased by a rise in temperature (application of the principle of Le Chatalier).

Acetylene usually is prepared by the action of water on calcium carbide.



$$C_2Ca + 2\,H_2O \longrightarrow C_2H_2 + Ca(OH)_2$$

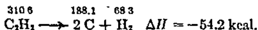
Calcium carbide is manufactured by heating a mixture of calcium oxide and carbon in an electric furnace to temperatures around 2000°.



$$3\,C + CaO \longrightarrow C_2Ca + CO$$

Acetylene may be prepared also by the general methods of dehalogenation and dehydrohalogenation described later.

Acetylene is thermodynamically unstable. Under ordinary conditions there is no decomposition, but when highly compressed it may explode under shock. When heated to about 800° it decomposes with explosive violence.



$$\overset{310.6}{C_2H_2} \longrightarrow \overset{188.1}{2\,C} + \overset{68.3}{H_2} \quad \Delta H = -54.2 \text{ kcal.}$$

The reaction, calculated from heats of combustion, is strongly exothermic. On this account the decomposition of a part promotes the decomposition of the rest. At lower temperatures, acetylene undergoes polymerization, mainly to benzene. This starts at about 400°; maximum conversion to benzene and other liquid products is realized at 650 to 700°. This is accompanied by decomposition to carbon and hydrogen.

Acetylene burns with a luminous, smoky, and very hot flame, for the heat of combustion is 312.4 kcal. Free carbon results from the decomposition of some of the acetylene at the high temperature of the flame. Special burners are necessary for obtaining complete combustion. Two fine streams of acetylene impinge at an angle so as to produce a flat, fan-shaped flame. This presents a large surface to the air and produces a brilliant light. Formerly acetylene was much used as an illuminant. Mixtures of acetylene and air

over the wide range of 3 to 82 per cent acetylene by volume are explosive when ignited.

Acetylene is important industrially. The very hot flame of the oxygen-acetylene torch is used for the cutting and welding of metals, especially steel. Also from acetylene many organic compounds are manufactured: (*a*) the chlorine addition products, acetylene dichloride and acetylene tetrachloride, much used as solvents; (*b*) acetaldehyde, from which other important chemicals, *e.g.*, acetic acid and acetone, can be manufactured; (*c*) unsaturated compounds such as vinyl chloride and vinyl acetate, the basis of an important group of synthetic resins and plastics; (*d*) vinyl acetylene, the basis of neoprene, a type of synthetic rubber.

Acetylene undergoes the reactions listed under general reactions of alkynes. The formation of metallic compounds should be discussed at this point, however, mainly because of the value of sodium acetylide in synthesis.

Acetylene as an Acid. When acetylene is passed into a solution of sodamide in anhydrous liquid ammonia, the monosodium salt, sodium acetylide, is formed.



$$NaNH_2 + C_2H_2 \longrightarrow C_2HNa + NH_3$$

The decomposition of sodamide by acetylene indicates that acetylene is a stronger acid than ammonia.

By the action of acetylene with ammoniacal silver or cuprous ion, gray insoluble silver acetylide or red cuprous acetylide is formed.



$$2\,Ag(NH_3)_2^+ + C_2H_2 \longrightarrow C_2Ag_2 + 2\,NH_3 + 2\,NH_4^+$$



$$2\,Cu(NH_3)_2^+ + C_2H_2 \longrightarrow C_2Cu_2 + 2\,NH_3 + 2\,NH_4^+$$

When dry these solids are liable to explode.

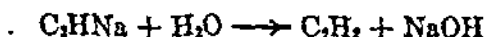
Under neutral or weakly acid conditions acetylene gives an insoluble precipitate with aqueous silver nitrate.



$$3\,AgNO_3 + C_2H_2 \longrightarrow AgNO_3 \cdot C_2Ag_2 + 2\,HNO_3$$

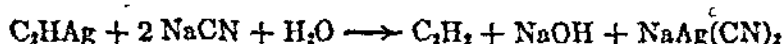
This reaction may be used for the quantitative determination of acetylene, by titration of the resulting nitric acid.

Metallic acetylides can be decomposed to yield acetylene. Sodium and calcium acetylides are decomposed by water alone.



$$C_2HNa + H_2O \longrightarrow C_2H_2 + NaOH$$

This indicates that water is a stronger acid than acetylene. The silver and cuprous salts are slowly decomposed by hydrochloric acid. They are decomposed more rapidly by aqueous sodium (or potassium) cyanide, due to the formation of the stable cyanide complex, as when silver cyanide or other insoluble silver salt dissolves in aqueous cyanide.



$$C_2HAg + 2\,NaCN + H_2O \longrightarrow C_2H_2 + NaOH + NaAg(CN)_2$$

Unsaturation enhances acidic properties. Although a very weak acid, acetylene is stronger than ethylene, which in turn is stronger than ethane.

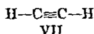
The acidic ionization constant of ethane has been estimated to have the exceedingly low value of 10^{-43}.

Structure of Acetylene. Bromine reacts readily, forming 1,1,2,2-tetrabromoethane.

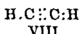


$$2\,Br_2 + C_2H_2 \longrightarrow Br_2CH{-}CHBr_2$$

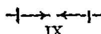
This and other reactions of acetylene are explained best by assuming that the two carbon atoms of acetylene are joined by a triple bond; each carbon atom in addition holds a hydrogen atom. Thus each carbon atom is quadrivalent, VII; the electronic structure is shown in VIII.



$H{-}C{\equiv}C{-}H$
VII



H.C⋮⋮C:H
VIII



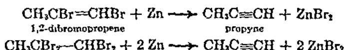
IX

The molecule of acetylene is linear (Fig. 3, p. 15). The triple bond represents a higher degree of unsaturation than the ethylenic double bond, as the characteristic reactions of acetylene hydrocarbons show. The high concentration of negative charges in the region between the carbon atoms makes the molecule essentially a double dipole, IX, the center of the molecule negatively charged, the two ends positively charged. This accounts for the weakly acidic nature of acetylene, which, however, is very much greater than that of an alkane.

Higher Alkynes. In Table 26 are listed some of the known alkynes and their constants. It is seen that $-\Delta H$ of hydrogenation of acetylene drops as methyl groups replace hydrogen atoms. For acetylene, $-\Delta H$ is 75.06 kcal., for methylacetylene, 69.70 kcal., and for dimethylacetylene, 65.58 kcal. The effect is greater than in the case of ethylene (p. 69). Also, $-\Delta H$ in going from alkyne to alkene is greater than that from alkene to alkane.

General Methods of Preparation of Alkynes. Two of these, (1) and (2) below, are similar to methods described under alkenes.

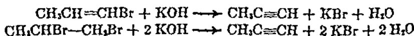
1. *Debromination of dibromoalkenes,* $C_nH_{2n-2}Br_2$, *or of tetrabromoalkanes,* $C_nH_{2n-2}Br_4$, by treatment with metallic zinc.



$$\underset{\text{1,2-dibromopropene}}{CH_3CBr{=}CHBr} + Zn \longrightarrow \underset{\text{propyne}}{CH_3C{\equiv}CH} + ZnBr_2$$
$$CH_3CBr_2{-}CHBr_2 + 2\,Zn \longrightarrow CH_3C{\equiv}CH + 2\,ZnBr_2$$

The bromine compounds usually are prepared from the corresponding alkynes. The method is of value mainly for purposes of purification.

2. *Dehydrobromination of bromoalkenes,* $C_nH_{2n-1}Br$, *or of dibromoalkanes,* $C_nH_{2n}Br_2$, by heating with potassium hydroxide, either as the solid or in some suitable organic solvent, or by heating with sodamide.



$$CH_3CH{=}CHBr + KOH \longrightarrow CH_3C{\equiv}CH + KBr + H_2O$$
$$CH_3CHBr{-}CH_2Br + 2\,KOH \longrightarrow CH_3C{\equiv}CH + 2\,KBr + 2\,H_2O$$

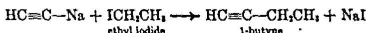
The dibromoalkanes usually can be obtained from the corresponding alkene by the action of bromine.

TABLE 26 | Constants of Some Alkynes

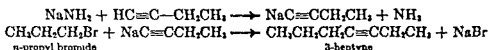
NAME		FORMULA	M.P. °C	B.P. °C	D_4^{20}	n_D^{20}	ΔH of		
I.U.C.	trivial						combustion [b,c]	formation [b,c]	hydrogenation [b]
THE LOWER 1-ALKYNES [a]									
Ethyne	Acetylene	$HC\equiv CH$	−81.8	−83			−310.61	+54.19	−75.06 [d]
Propyne	Methylacetylene	$HC\equiv CCH_3$	−101.5	−23.23			−463.11	+44.32	−69.70 [d]
1-Butyne	Ethylacetylene	$HC\equiv CCH_2CH_3$	−122	8.6	0.668 [e]		−620.86	+39.70	
1-Pentyne	n-Propylacetylene	$HC\equiv C(CH_2)_2CH_3$	−98	39.7	.6950	1.3860	−778.03	+34.50	
1-Hexyne	n-Butylacetylene	$HC\equiv C(CH_2)_3CH_3$	−124	72	.7195	1.3990	−935.45		
1-Heptyne	n-Amylacetylene	$HC\equiv C(CH_2)_4CH_3$	−80	99.6	.7332	1.4083	−1092.89		
1-Octyne	n-Hexylacetylene	$HC\equiv C(CH_2)_5CH_3$	−70	126.0	.7469	1.4169	−1250.31		
1-Nonyne	n-Heptylacetylene	$HC\equiv C(CH_2)_6CH_3$	−65	151	.763	1.425	−1407.78		
1-Decyne	n-Octylacetylene	$HC\equiv C(CH_2)_7CH_3$	−36	182	.772 [f]	1.436 [f]	−1562.62		
OTHER ALKYNES									
2-Butyne	Dimethylacetylene	$CH_3C\equiv CCH_3$	−24	26.69	.6937	1.3939	−596.88	+35.37	−65.58 [d]
2-Pentyne	Methylethylacetylene	$CH_3C\equiv CCH_2CH_3$	−101	55	[illegible] [g]	1.4045 [g]		+30.80	
2-Hexyne	Methyl n-propylacetylene	$CH_3C\equiv C(CH_2)_2CH_3$	−92	84	[illegible]	1.4140			
3-Hexyne	Diethylacetylene	$CH_3CH_2C\equiv CCH_2CH_3$	−51	81	.7255	1.4121			
4-Octyne	Di n-propylacetylene	$CH_3(CH_2)_2C\equiv C(CH_2)_2CH_3$		130.6	.7479	1.4225			
5-Decyne	Di n-butylacetylene	$CH_3(CH_2)_3C\equiv C(CH_2)_3CH_3$		175.3	[illegible] [h]	1.4311 [h]			

[a] Data other than thermodynamic from *Physical Constants of Hydrocarbons*, Vol. I, by G. Egloff, Reinhold Publishing Corp., New York, 1939.
[b] In the gaseous state, kilocalories per mole.
[c] At 25° C data from Circular C461, National Bureau of Standards, Washington, D. C., 1947.
[d] At 82° C (Kistiakowsky *et al.*, 1939).
[e] [illegible]
[f] [illegible]
[g] At 21°.
[h] At 25°.

3. *Reaction of a monobromo (or monoiodo) alkane with a sodium alkynide.*

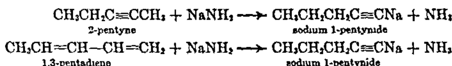


The products from such reactions are 1-alkynes, that is, acetylene hydrocarbons having the triple bond at the end of the chain. Sodium salts may be obtained from these by the action of sodamide, and these may react with more ethyl iodide, or even with some other bromo (or iodo) alkane.

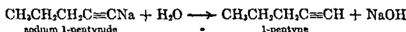


This is one of the most valuable synthetic methods for the preparation of the higher alkynes. A necessary precaution is the exclusion of moisture.

4. *Isomerization of isomeric alkynes or alkadienes to 1-alkynes, by heating with sodamide.*

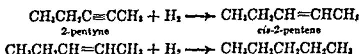


The ability of 1-pentyne to form the stable sodium salt causes a quantitative conversion, for the three hydrocarbons are slowly interconvertible at elevated temperatures. Addition of water liberates the alkyne.



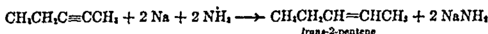
General Reactions of Alkynes. The principal reactions, like those of the alkenes, are addition, including hydrogenation and hydration. Unsymmetrical additions conform to Markownikoff's rule. Other reactions are substitution and salt formation. The addition reactions are more exothermic than the corresponding reactions of alkenes. Thus from bond energies the ΔH of hydrogenation of a gaseous alkyne to a gaseous alkene is -48 kcal., and that of an alkene to an alkane is -30 kcal. The difference is somewhat greater in those cases where the addition product of the first reaction is stabilized by resonance, as when hydrogen chloride adds to form vinyl chloride (Chap. 8). Reversibility of an alkyne addition reaction, therefore, cannot be accomplished as easily as the similar alkene reaction. Thus the preparation of alkynes by dehalogenation or by dehydrohalogenation usually is more difficult to accomplish than the preparation of alkenes by similar means.

1. *Hydrogenation.* Alkynes add two molecules of hydrogen in contact with an active platinum catalyst at room temperature. With a palladium or Raney nickel catalyst at room temperature the reaction can be controlled, so that either one or two moles of hydrogen can be added, due to the fact that the rate of addition of the second molecule is much lower.



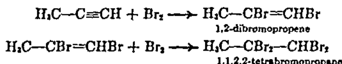
Dialkyl acetylenes yield the *cis*-olefins.

Reduction of alkynes can be accomplished by the action of sodium in liquid ammonia. Under these conditions dialkyl acetylenes yield *trans*-olefins. The reduction does not continue.

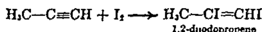


The experimentally determined heats of hydrogenation of a few alkynes to the corresponding alkanes are given in Table 26. From these values and the heats of hydrogenation of the corresponding alkenes to the alkanes (Table 24, p. 66) can be calculated the heats of hydrogenation of the alkynes to the alkenes. In the case of acetylene this is 42.3 kcal., a value significantly larger than the 32.7 kcal. involved in the hydrogenation of ethylene to ethane.

2. *Addition of halogens.* One or two molecules of chlorine or bromine may add.



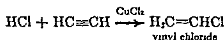
In the presence of oxygen the addition of a second molecule of bromine may be slow and incomplete. One mole of iodine adds.



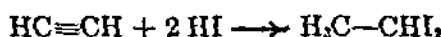
3. *Addition of hypohalous acids.* Hypochlorous or hypobromous acid adds to the triple bond, producing a dihalogenated ketone, with the two halogen atoms on the same carbon atom (acetylene yields a dihalogenated acetaldehyde).



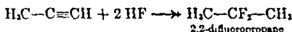
4. *Addition of hydrogen halides.* One molecule of hydrogen halide adds fairly readily. The rates are in the order HI > HBr > HCl. A catalyst is desirable with hydrogen chloride (cupric or mercuric chloride) or with hydrochloric acid (mercuric chloride).



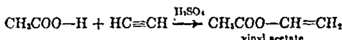
Vinyl chloride is important as the basis of a type of synthetic plastic (Chap. 8). A second molecule of hydrogen halide may add to the vinyl halides For example, concentrated hydriodic acid reacts at 100° to yield ethylidene iodide.



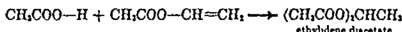
Acetylene and higher alkynes react when passed into anhydrous liquid hydrogen fluoride.



5. *Addition of organic acids.* One molecule may add, in the presence of a strong mineral acid, *e.g.*, hydrogen sulfate, as in the addition of acetic acid to acetylene.

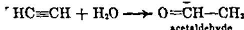


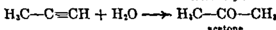
Acetylene adds two molecules of acetic acid, but the corresponding derivatives of many higher homologs are unstable.



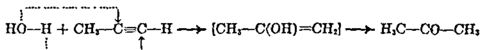
Vinyl acetate is the basis of an important synthetic plastic (Chap. 15).

6. *Hydration.* Acetylene adds water when in contact with dilute sulfuric acid and mercuric sulfate, yielding acetaldehyde $CH_3CH{=}O$. The reaction requires catalysis by both acid and mercuric ion. Acetylene homologs undergo the addition reaction more readily, sometimes in presence of dilute sulfuric acid alone. They are converted to ketones.



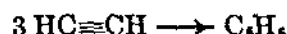


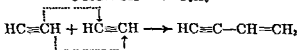
The first step probably is the formation of an unstable intermediate (see Vinyl Alcohol, Chap. 11) which spontaneously changes to the final product.

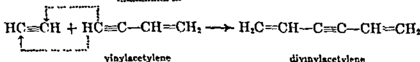


The hydration of acetylene to acetaldehyde, known for many decades, became important industrially during World War I.

7. *Polymerization.* Alkynes undergo polymerization. Acetylene when passed through a hot tube at temperatures of 650 to 700° polymerizes to a complex mixture of aromatic compounds, of which benzene, C_6H_6, is one. When in contact with a suitable cuprous catalyst at ordinary temperature, acetylene is converted into the dimer, vinylacetylene, $H_2C{=}CH{-}C{\equiv}CH$, and the trimer, divinylacetylene, $H_2C{=}CH{-}C{\equiv}C{-}CH{=}CH_2$.

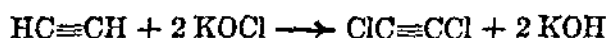






One effective catalyst is cuprous ammonium chloride. The formation of vinylacetylene is the first step in the production of chloroprene, the basis of neoprene, a type of synthetic rubber (p. 92). Cyclic polyenes (cyclo-octatetraene, for example) are formed, with special compounds of nickel as catalyst.

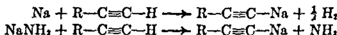
8. *Substitution.* The halogens react under alkaline conditions to form substitution products. For example, when acetylene is passed into aqueous potassium hypochlorite, the product is dichloroacetylene.



With aqueous potassium hypobromite, dibromoacetylene is formed; diiodoacetylene is obtained when aqueous potassium hypochlorite is added to aqueous potassium triiodide containing dissolved acetylene. This type of reaction is limited to alkynes having the group, C≡C—H.

9. *Metallic alkynides.* Like acetylene, 1-alkynes (monoalkylated acetylenes) form sodium, cuprous, and silver salts. The cuprous salts, R—C≡C—Cu (usually yellow) and the silver salts, R—C≡C—Ag (usually colorless) are formed by the action of aqueous ammoniacal solutions of the respective ions, as in the case of the corresponding acetylene compounds. The formation of either of these two insoluble solids often is used as a means of distinguishing 1-alkynes from other types of hydrocarbons.

Sodium alkynides can be obtained from 1-alkynes by the action of sodamide or of metallic sodium in liquid ammonia. The latter has the disadvantage of reducing some of the alkyne to the alkene.

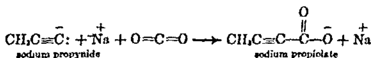


A sodium alkynide is an ionic compound, and is composed of positive sodium and negative alkynide ions. Negative ions in which a carbon atom carries the negative charge often are called **carbanions.** Sodium alkynides are rapidly and completely decomposed by water, owing to the strong attraction of the negatively charged carbon atom for a proton.

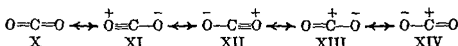


Water is a much stronger acid than the alkyne. If it were not, the alkyne would react with the base to form the sodium salt.

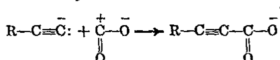
The sodium alkynides are of use in synthesis. They react with: (*a*) alkyl halides, to yield disubstituted acetylenes, as described under the preparation of alkynes; (*b*) carbon dioxide, to yield acids containing a triple bond; and (*c*) many compounds (aldehydes and ketones, Chap. 17) containing a C=O double bond, to yield unsaturated alcohols



The reaction of carbon dioxide with a sodium alkynide takes place rapidly. *In the alkynide ion a carbon atom has an unshared electron pair, and on this account exerts a strong attraction for the positive nucleus of some other atom,* as, for example, the proton in compounds which possess acidic properties greater than that of the alkyne. Because of this attraction such a carbon atom is sometimes designated as **nucleophilic** (Gr. *philos*, loving). The structure of carbon dioxide involves not only the three unexcited structures, X, XI, and XII, but also the excited structures, XIII and XIV, to a much less extent, of course, because they are much less stable.

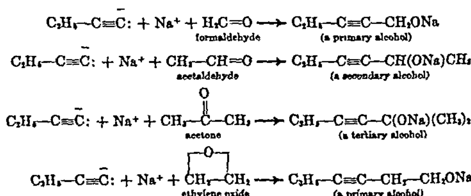


In XIII and XIV the carbon atom is deficient in electrons and carries a formal positive charge. Such an atom is called electrophilic because it strongly attracts electrons. The reaction of carbon dioxide with an alkynide ion can be regarded as the attachment of the positive carbon nucleus of carbon dioxide to the unshared electron pair of the carbanion.



The sodium ion plays no part in the reaction.

The reactions of sodium alkynides with a number of organic compounds are similar to those of organometallic compounds described in Chapter 9. Sodium propynide is taken as an example.



The products are sodium salts of unsaturated alcohols, which in order are, 2-pentyne-1-ol, 3-hexyne-2-ol, 2-methyl-3-hexyne-2-ol, and 3-hexyne-1-ol.

ALKADIENES

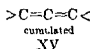
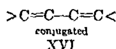
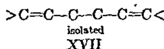
The alkadienes, commonly called diolefins, are isomeric with the acetylene hydrocarbons. The molecule possesses two double bonds in place of a triple bond. Naming according to the I.U.C. system is described on page 77. In Table 27 are the boiling points and names of a few diolefins.

TABLE 27 **Constants of Some Dienes** [a]

NAME: I.U.C.	NAME: trivial	FORMULA	M.P. °C	B.P. °C	D_4^{20}	n_D^{20}	ΔH of combustion [b] kcal./mole	ΔH of formation [b] kcal./mole	ΔH of hydrogenation [b] kcal./mole
Propadiene	Allene	$CH_2=C=CH_2$	−136.1	−34.34			−465.2 [e]	46.48	−71.28 [d]
1,2-Butadiene	Methylallene	$CH_2=C=CHCH_3$		10.3					
1,3-Butadiene	Erythrene	$CH_2=CHCH=CH_2$	−108.7	−4.75	0.650 [e]	1.422 [e]	−608.3 [e]	27.29	−57.06 [d]
1,2-Pentadiene	Ethylallene	$CH_2=C=CHCH_2CH_3$		44.7	.6904	1.4191			
1,3-Pentadiene	Piperylene	$CH_2=CHCH=CHCH_3$	−87.7	41.85	.680		−762.7 [e]	20.32	−54.11 [d]
1,4-Pentadiene		$CH_2=CHCH_2CH=CH_2$	−148.1	26.3	.6453	1.4304	−769.4 [e]	27.00	−60.79 [d]
2-Methyl-1,3-butadiene	Isoprene	$CH_2=C(CH_3)CH=CH_2$	−146.8	34.08	.6808	1.42158	−760.1 [f]	17.66	−53.36 [g]
1,5-Hexadiene	Biallyl	$CH_2=CH(CH_2)_2CH=CH_2$	−140.8	59.57	.6899	1.4034	−926.3 [e]	20.6	−60.52 [d]
2,3-Dimethyl-1,3-butadiene	Methylisoprene	$CH_2=C(CH_3)—C(CH_3)=CH_2$	−76.0	68.70	.7263	1.4390	−919.7 [e]	14.0	−53.87 [d]

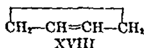
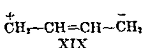
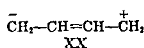
[a] Data other than thermodynamic from *Physical Constants of Hydrocarbons*, Vol. I, by G. Egloff, Reinhold Publishing Corp., New York, 1939.
[b] In the gaseous state.
[c] Calculated from ΔH of hydrogenation, but without making temperature correction.
[d] At 82° C (Kistiakowsky, *et al.*, 1938).
[e] At −6°.
[f] In the liquid state, −754.64 kcal.
[g] Calculated from the heat of combustion.

Three types of systems containing two double bonds are recognized; *viz.*, **cumulated,** *in which the two double bonds are attached to the same carbon* atom, **conjugated,** in which they are attached to adjacent carbon atoms, and **isolated,** in which they are attached to carbon atoms separated from each other by one or more saturated carbon atoms:

The relative stabilities of these systems are indicated by the respective heats of hydrogenation. From the data of Table 27, it is seen that ΔH of hydrogenation of the two double bonds of allene (cumulative) is -70 kcal., of 1,3-butadiene (conjugated) is -57 kcal., and of biallyl (isolated) is -60 kcal. Thus each isolated double bond of biallyl is essentially equivalent to the double bond of 1-butene (-30 kcal.). However, the two bonds of allene are less stable by 10 kcal., and those of butadiene are more stable by 3 kcal. The greater instability of the double bonds of allene can be ascribed to the strain connected with the presence of two double bonds on one carbon atom.

The greater stability of the double bonds of 1,3-butadiene is ascribed to resonance. Structural determinations by means of electron diffraction show that the distance between the two middle carbon atoms is 1.46 Å. This is 0.08 Å shorter than the normal single-bond distance. This is interpreted as indicating that the bond possesses some double-bond character. The complete structure of butadiene involves not only the usual form, Table 27, but also, to a much less extent, XVIII, XIX, and XX.

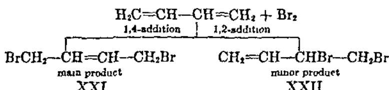
Of these three, XIX and XX contribute least to the overall structure, owing to their lower stabilities, but on the other hand they are important in connection with chemical reactivity. The contribution of XVIII, XIX, and XX to the butadiene structure accounts for: (*a*) the double-bond character (although weak) of the carbon-to-carbon single bond and (*b*) the resonance energy (although small) of butadiene.

General Preparation of Diolefins. They may be obtained by some of the general methods applied to the preparation of olefins, *viz.*, dehydration of alcohols (in this case unsaturated alcohols or dihydric alcohols) and dehydrohalogenation of halogen compounds. Dehydrogenation of alkanes or of alkenes is important industrially. However, since these reactions are strongly endothermic, a high temperature is necessary (see Table 21, p. 55). Other reactions, such as polymerization and decomposition, also take place under these conditions, consequently careful control of conditions and special catalysts are necessary.

Reactions of Dienes. The most important dienes are the conjugated dienes. Isoprene is important in connection with a number of natural

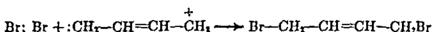
products, for example, the terpenes (Chap. 43) and natural rubber, which are considered to be composed of two or more isoprene units. Butadiene is important in connection with synthetic rubber (p. 92). The most important reactions of conjugated dienes are addition and the related reaction of polymerization.

1. *Addition.* Bromine reacts readily with 1,3-butadiene. The main product is 1,4-dibromo-2-butene, XXI, and a by-product is 3,4-dibromo-1-butene, XXII.



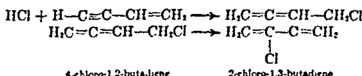
The formation of XXI is somewhat unexpected, for one would expect the bromine to be added to one of the bonds only. The result was explained many years ago by Thiele on the assumption that the two middle carbon atoms, being unsaturated, tended to mutually saturate each other, and thus leave the terminal atoms more unsaturated.

The course of the reaction is now explained in terms of resonance. The contributions of the activated forms, XIX and XX, to the overall structure of 1,3-butadiene put a partial charge on each of the terminal carbon atoms. When bromine reacts, one mechanism is believed to operate in such a way that the electron pair joining the two bromine atoms in the bromine molecule goes with one of the atoms, with the result that one bromine atom tends to react as a negative ion, the other as a positive ion.



Owing to the negative charge on a carbon atom of the butadiene molecule the electrons are available for bond formation. The reaction in which XXI is the product is called 1,4-addition from the relative positions of the two bromine atoms in XXI, and the other reaction is called 1,2-addition, from the relative positions of the two bromine atoms in XXII. Both XXI and XXII react with a second molecule of bromine, but more slowly. The product from each is 1,2,3,4-tetrabromobutane.

Other conjugated systems react by 1,4-addition. Not only may halogens add, but also hydrohalic acids. Thus vinyl acetylene (p. 84) reacts with hydrogen chloride. The first product, 4-chloro-1,2-butadiene, is unstable and rearranges to the final product, chloroprene (2-chloro-1,3-butadiene).



Chloroprene is important in connection with synthetic rubber.

2. *Polymerization.* One of the first methods for polymerizing butadiene involved the use of metallic sodium. The polymerization induced by this reagent is believed to proceed via a free radical mechanism, the free radical resulting from the passage of an electron from sodium to butadiene, or from the formation of a sodium compound by the addition of sodium to butadiene.

$$Na\cdot + H_2C{=}CH{-}CH{=}CH_2 \longrightarrow Na^+ + H_2\bar{C}{-}CH{=}CH{-}\dot{C}H_2$$

The butadiene free radical ion reacts rapidly with another butadiene molecule, and the reaction proceeds by a 1,4-addition.

$$H_2\bar{C}{-}CH{=}CH{-}\dot{C}H_2 + CH_2{=}CH{-}CH{=}CH_2 \longrightarrow$$
$$H_2\bar{C}{-}CH{=}CH{-}CH_2{-}CH_2{-}CH{=}CH{-}\dot{C}H_2$$

The resulting free radical ion of the dimer also can react rapidly with a third molecule, and so on until the free radical character is lost by combination with some other free radical or by loss of the sodium atom. The final result is a long chain polymer, a so-called linear polymer. In general the polymerization reaction is a 1,4-addition. Many other dienes polymerize, for example, isoprene, chloroprene, and 2,3-dimethyl-1,3-butadiene (methylisoprene).

Polymerization may be induced in other ways. Oxygen causes a slow polymerization. Organic peroxides are much employed now as polymerization agents. These are unstable and when they decompose, free radicals are formed. A free radical can initiate polymerization by combining with butadiene. The resulting butadiene free radical combines with a second molecule of butadiene, and so on. Oxygen acts through the ability to form organic hydroperoxides, and these decompose, giving free radicals.

Isoprene, 2-Methyl-1,3-butadiene, C_5H_8. This is an important diolefin. It is formed, along with many other hydrocarbons, when natural rubber is pyrolyzed and may be obtained by the pyrolysis of turpentine also. It has been prepared by dehydration of dihydroxyisopentane and by the action of hot bases on dichloroisopentane, 2,4-dichloro-2-methylbutane.

$$\underset{\text{2,4-dichloro-2-methylbutane}}{CH_3{-}\underset{\substack{|\\CH_3}}{C}Cl{-}CH_2{-}CH_2Cl} + 2\,NaOH \longrightarrow \underset{\text{isoprene}}{CH_2{=}\underset{\substack{|\\CH_3}}{C}{-}CH{=}CH_2} + 2\,NaCl + 2\,H_2O$$

Isoprene is important because it is regarded as the fundamental unit of structure of many naturally occurring substances, among them the terpenes, the carotenes, and rubber.

Natural Rubber, Caoutchouc, $(C_5H_8)_x$. The principal source of rubber is the rubber tree, *Hevea braziliensis.* This tree is indigenous to Brazil, from which country, until as late as 1910 most of the rubber of commerce came. In 1876 about 70,000 seeds of this tree were transported to England where sprouting was carried out at Kew Gardens. Two months later many seedlings were sent to Ceylon. Selection over a period of years in Ceylon and in the East Indies resulted in the development of strains much superior to the original. World production of rubber increased from 94,000

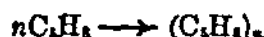
long tons in 1910 to 1,390,000 long tons in 1940. Of the last, less than 2 per cent came from Brazil. The annual consumption in the United States was then about 800,000 tons. During 1951 the production of natural rubber was 1,850,000 long tons and the U. S. consumption of all rubber was 1,280,000 long tons.

Rubber is present in many other plants, for example, dandelion, fig, goldenrod, guayule, and milkweed. Generally the amount is too small to be of value commercially. However guayule was grown successfully in California for many years after 1925.

Rubber is present in the sap of the rubber tree. This sap, called **latex**, is a milky fluid. It is an emulsion containing about 35 per cent of rubber, and this can be precipitated by the addition of an acid. The emulsion can be stabilized by the addition of ammonia, and in this way can be kept for a long time or shipped long distances. Latex can be concentrated or "creamed" by the addition of a suitable material, usually a gum or a salt of a polyuronic acid (alginic acid). The rubber content of the creamed latex is about double that of latex.

Rubber becomes sticky when warmed, but it loses this undesirable quality when it is vulcanized. This usually is done by heating with sulfur, a process discovered by Goodyear in 1839. Vulcanization may lead to a soft product, such as that used in automobile tires, or to a much harder material, depending upon the amount of sulfur added. An **accelerator** is added to hasten the process; it acts catalytically. An accelerator is a complex organic compound, usually containing both sulfur and nitrogen, for example, diphenylthiourea.

When strongly heated, rubber is decomposed and a number of volatile hydrocarbons are formed, among them isoprene. Since the empirical formula of rubber also is C_5H_8, chemists early considered rubber to be a polymer of isoprene. This view is supported by the observation that isoprene slowly changes into an amorphous rubberlike product, a true polymer.

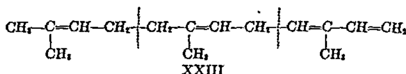


$$nC_5H_8 \longrightarrow (C_5H_8)_n$$

This laboratory polymer lacks many of the desirable properties of natural rubber and although chemists have experimented extensively, attempts to obtain from isoprene a polymer having satisfactory commercial qualities have not been successful.

Natural rubber is a complex mixture of polyprenes of varied molecular weight. Aside from a few per cent of lower material and about 15 per cent of material insoluble in both hexane and chloroform, the main components of rubber have molecular weights in the approximate range, 60,000 to 190,000. The average molecular weight of rubber varies from 130,000 to 180,000.

The structure of rubber has been deduced from the nature of the products obtained on degradation, in particular ozonolysis and oxidation, and from other studies. The arrangement of carbon atoms follows in general a regular pattern, XXIII.



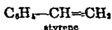
In XXIII there is a succession of isoprene units. This unit of five carbon atoms, one of which is in a methyl side chain, is repeated many times. For a molecule with a molecular weight of about 150,000 the section between the dotted lines is ...

about 2200 times. The structure of XXIII is exactly the one expected if isoprene underwent polymerization by 1,4-addition (p. 90). Owing to the presence of double bonds rubber is attacked by strong oxidizing agents. Oxygen of the air causes slow deterioration also.

During vulcanization sulfur combines with rubber so as to form a sulfur bridge between molecules Only a small per cent of sulfur is needed to overcome the undesirable property of tackiness. The elastic properties, which are at a maximum with a small amount of sulfur, decrease as the proportion of sulfur is increased and give way to a hard, nonelastic product. An effect of cross linkage between linear polymers is an increase in hardness and this is observed also in many other kinds of polymeric materials.

Synthetic Rubber. In connection with rubber the word synthetic has a different meaning from the usual one, for in general it connotes a substance produced in the laboratory and identical with the natural product. The expression, synthetic rubber, has come to mean an artificial product having some or many of the desirable properties of natural rubber. Starting about 1908 much intensive research was carried out, mainly in England and Germany, on the polymerization of 1,3-butadiene, isoprene, and methylisoprene (p. 87). It was early found that polymerization could be induced by metallic sodium. When the average yearly price of natural rubber later dropped from one dollar in 1910 to less than twenty cents in the early 1920's, interest in synthetic rubber lagged. However in the meantime an inferior product was developed in Germany during World War I by polymerizing methylisoprene. It was called methyl rubber. Surprisingly enough the problem was solved when the price was about six cents, not far above the historic low.

The first commercially valuable synthetic rubber was neoprene ("Duprene"), obtained by the polymerization of chloroprene (p. 89), first announcement of which was made in the United States in 1931. Then followed other successes. The Germans developed the Buna rubbers, bu for butadiene, na for sodium. They are copolymers from butadiene and some other unsaturated compound. The two principal products are Buna S and Buna N, having styrene and acrylonitrile, respectively, as the other component.





An important improvement is emulsion polymerization. Here the organic materials are emulsified with water and polymerization is induced by organic peroxides, originally benzoyl peroxide. Recently (1948) the quality of the polymer has been further improved by cold polymerization.

Isobutylene, copolymerized with a small amount (2–5%) of butadiene gives a polymeric product called butyl rubber. Many other unsaturated compounds also give polymers and some of these have elastic properties.

During World War II the supply of natural rubber from the East Indies was cut off. Enough development had taken place in the United States prior to 1940 to lay the foundation for a synthetic rubber industry. The work was greatly expanded with government assistance. Yearly production rose from about 40,000 tons in 1941 to 900,000 tons in 1945. This involved enormous increase in the manufacture not only of synthetic rubber but also of the main raw materials, butadiene and styrene. Production later declined, as natural rubber again became available after the war and then rose later to 850 000 long tons in 1951. Synthetic rubber will remain as an im-

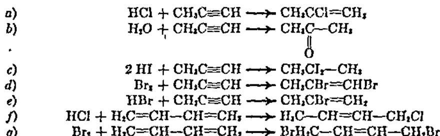
portant industrial product, partly as a guarantee against another shortage, partly as a product having merit in its own right. Various names were given to different products at first, but later these were designated as GR (government rubber), for example, GRS for Buna S.

Synthetic rubber is more saturated (less unsaturated) than natural rubber. Butyl rubber is the most saturated, having only a few per cent unsaturation from the small amount of butadiene added. As a result of greater saturation synthetic rubber in general is more resistant to deterioration than is natural rubber.

The four principal types of synthetic rubber produced in the United States are GRS, Buna N, neoprene, and butyl. GRS is best for automobile tires, and on this account makes up the bulk of the production. Buna N in elastic properties is closer to natural rubber than the others, and is used in the manufacture of numerous objects. Neoprene (GRM), is used in the manufacture of hose and other objects exposed to gasoline or other organic solvent. It is the most expensive synthetic rubber. Butyl (GRI), because of its imperviousness to gases, is unsurpassed for inner tubes.

PROBLEMS

1. Show how ΔH for the following reactions in the gas phase may be calculated from bond energies and resonance energies. To what extent do the actual values differ from these when the reactions are carried out at 25°?



a) $HCl + CH_3C{\equiv}CH \longrightarrow CH_3CCl{=}CH_2$

b) $H_2O + CH_3C{\equiv}CH \longrightarrow CH_3C({=}O){-}CH_3$

c) $2\,HI + CH_3C{\equiv}CH \longrightarrow CH_3CI_2{-}CH_3$

d) $Br_2 + CH_3C{\equiv}CH \longrightarrow CH_3CBr{=}CHBr$

e) $HBr + CH_3C{\equiv}CH \longrightarrow CH_3CBr{=}CH_2$

f) $HCl + H_2C{=}CH{-}CH{=}CH_2 \longrightarrow H_3C{-}CH{=}CH{-}CH_2Cl$

g) $Br_2 + H_2C{=}CH{-}CH{=}CH_2 \longrightarrow BrH_2C{-}CH{=}CH{-}CH_2Br$

2. Show how to calculate ΔH of formation of the following from the data on the heats of hydrogenation:

a) propyne
b) 2-butyne
c) propadiene
d) 1,3-butadiene
e) 1,3-pentadiene
f) 1,4-pentadiene

3. Write balanced equations for the reactions involved in a practical laboratory preparation from acetylene and any other compounds of:

a) 1-butyne
b) 1-pentyne
c) 2-pentyne
d) 2-hexyne
e) 3-hexyne
f) 2-heptyne
g) 5-methyl-1-hexyne
h) 5-methyl-2-hexyne
i) 2-methyl-3-hexyne
j) 1-nonyne

4. Write balanced equations for the reactions involved (stating conditions) in a laboratory preparation of 1-hexyne, starting with the following, and using any other reagents:

a) 2-hexyne
b) 1,2-dibromohexane
c) 1,1,2,2-tetrabromohexane
d) 2-bromohexane
e) 1-hexene
f) 2,3-dibromohexane
g) 1-pentyne
h) 1-iodohexane
i) 1,3-hexadiene
j) 1-bromobutane

5. Starting with 1-butyne and using any reagents, indicate the sequence of operations (reagents and conditions) for a satisfactory laboratory preparation of the following in a reasonably pure state:

a) 2-chloro-1-butene
b) 2-iodo-1-butene
c) 2,2-diiodobutane
d) 1,2-dibromo-1-butene
e) 1,1,2,2-tetrachlorobutane
f) 1-butene
g) 2-bromobutane
h) 3,4-dimethylhexane
i) 5-methyl-3-heptyne
j) 1,2-dibromobutane
k) $CH_3CH_2COCH_3$
l) $CH_3CH_2C{\equiv}C{-}COOH$
m) 3-hexyne
n) 1-hexyne

6. Starting with 2-butyne, indicate the sequence of operations (reagents and conditions) for a satisfactory laboratory preparation of the following in a reasonably pure state:

a) 2-bromo-2-butene
b) 2,3-dichloro-2-butene
c) 1-butyne
d) 2-butene
e) 2,3-dibromobutane
f) 2-chloro-2-butene
g) 2-iodo-2-butene
h) 2-iodobutane
i) 2,2,3,3-tetrabromobutane
j) 2-bromo-2-iodobutane
k) 2,3-dichloro-2,3-dibromobutane
l) 2-hydroxybutane

7. Write balanced equations for the reactions of 1-hexyne with the following and name the organic compound formed:

a) hydriodic acid (one mole)
b) hydriodic acid (two moles)
c) bromine (one mole)
d) bromine (two moles)
e) bromine (one mole, in presence of aqueous sodium hydroxide)
f) water (in presence of sulfuric acid)
g) hydrogen (one mole, in presence of nickel)
h) hydrogen (two moles, in presence of nickel)
i) sodamide (in liquid ammonia)
j) sodium and liquid ammonia

8. Show by means of suitable names or formulas the possible isomeric acyclic compounds of the formula:

a) C_4H_6
b) C_4H_5Cl
c) $C_4H_6Br_2$
d) C_3H_3Cl
e) $C_3H_2Cl_2$
f) C_4HCl_2Br

9. Describe a convenient chemical test, stating reagent, conditions, solvent (if any), and readily detectable change, that serves to distinguish between:

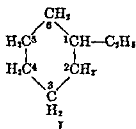
a) *n*-hexane and 1-hexene
b) 1-hexene and 1-hexyne
c) 1-heptyne and 2-heptyne
d) 1-butyne and 1,3-butadiene
e) diethylacetylene and *n*-butylacetylene

CHAPTER 7

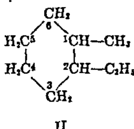
Alicyclic Hydrocarbons, Cycloalkanes, Cycloparaffins, C_nH_{2n}

For each normal paraffin above ethane there is a theoretically possible cyclic hydrocarbon in which the two terminal carbon atoms of the acyclic hydrocarbon are joined together. Such a hydrocarbon is said to possess a ring structure, and is called a cycloparaffin, or cycloalkane, sometimes a closed-chain hydrocarbon, as distinct from the acyclic or open-chain hydrocarbon. It belongs to the group of alicyclic hydrocarbons, *i.e.*, aliphatic cyclic hydrocarbons, as distinct from aromatic hydrocarbons (Chap. 27). Alicyclics may be saturated or unsaturated.

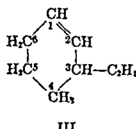
Nomenclature. The name of a cycloalkane is derived from the corresponding alkane, with the prefix cyclo (see Table 28). In case an alkyl side chain is attached to the ring, the side chain is named as a substituent. Thus I is ethylcyclohexane. In case two side chains are attached, the numbering starts at the smaller side chain. Thus II is 1-methyl-2-ethylcyclohexane. In case a double bond is present, numbering starts there. Thus III is 3-ethylcyclohexene.



I



II



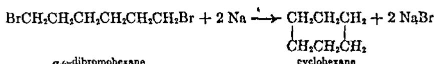
III

The equivalence of positions in any one cycloalkane simplifies isomerism of derivatives. There are two structurally isomeric disubstitution products of cyclopropane, three of cyclobutane and cyclopentane, four of cyclohexane and cycloheptane, etc. However, because of stereoisomerism, there are actually more than these (Chap. 26).

Occurrence. Hydrocarbons having rings of five and six carbon atoms are present in many petroleums, especially those of the asphaltic-base type. They are often called "naphthenes." Many other hydrocarbons having rings of six carbon atoms belong to the group of terpenes and are present in many

essential oils (Chap. 43). Numerous alcohols and ketones of these are present in essential oils also. The six-membered carbon ring is thus the most important of the various cycloalkane systems.

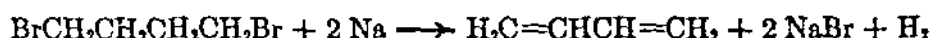
Preparation of Cycloalkanes. The Wurtz synthesis from α,ω-dibromoalkanes (dibromides with bromine atoms attached to terminal carbon atoms) can be applied to the synthesis of a few cycloalkanes, *viz.*, cyclopropane, cyclopentane, and cyclohexane.



$$BrCH_2CH_2CH_2CH_2CH_2CH_2Br + 2\,Na \longrightarrow \begin{matrix} CH_2CH_2CH_2 \\ | \quad\quad | \\ CH_2CH_2CH_2 \end{matrix} + 2\,NaBr$$

α,ω-dibromohexane cyclohexane

Instead of cyclobutane, 1,4-dibromobutane yields butadiene.



$$BrCH_2CH_2CH_2CH_2Br + 2\,Na \longrightarrow H_2C{=}CHCH{=}CH_2 + 2\,NaBr + H_2$$

α,ω-Dibromides of heptane and higher hydrocarbons yield mainly high molecular weight compounds (see p. 99). In order to obtain closure of the cyclobutane and other rings, synthetic methods of more complicated nature can be used (Chap. 26).

Physical Properties of Cycloalkanes. Some of these are listed in Table 28. It is interesting that, in comparison to normal alkanes, cycloal-

TABLE 28 | Constants of Some Cycloalkanes

I U C. NAME	TRIVIAL NAME	FORMULA	SP GR. 20°/4°	M P °C	BOILING POINT °C			ΔH OF COMBUSTION [a]		
					cycloalkane	normal alkane	difference	per mole	per CH_2	dev from normal [b]
[illegible]	[illegible]	[illegible]	[illegible]	−126.9	−33	−42.2	9.2	−505.5	−168.5	−11.1
[illegible]	[illegible]	[illegible]	[illegible]	−80	13	−0.5	13.5	−662.5	−165.6	−8.2
[illegible]	[illegible]	[illegible]	[illegible]	−94.4	49.3	36.0	13.3	−793.6	−158.7	−1.3
[illegible]	[illegible]	[illegible]	[illegible]	6.5	80.9	68.7	12.2	−944.5	−157.4	0.0
[illegible]	[illegible]	[illegible]	[illegible]	−12	118	98.4	19.6	−1108.0	−158.3	−0.9
[illegible]	[illegible]	[illegible]	[illegible]	14.4	149	125.6	23.4	−1268.8	−158.6	−1.2

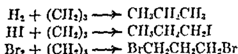
[a] For the gaseous state, in kilocalories per mole
[b] Taking ΔH of combustion of methylene as −157.4 kcal, Table 22
[c] At −40°.
[d] At 0°.

kanes are heavier and have higher boiling points. Also, the lower members have, per methylene, higher heats of combustion. The significance of this is pointed out later in connection with the Baeyer strain theory.

Reactions. Cycloalkanes, except in the case of cyclopropane and cyclobutane, resemble alkanes closely in chemical reactivity. They undergo substitution with chlorine or bromine to yield the corresponding chloro or bromo cycloalkane. They are not altered by the usual oxidizing or reducing agents.



Cyclopropane undergoes some reactions which bear a resemblance to those of alkenes. It reacts with hydrogen at 80° in the presence of a nickel catalyst, with hydriodic acid (when heated), and with bromine.



In these reactions the cyclopropane ring is opened and the product is propane or one of its derivatives. It will be recalled that the double bond of propylene is opened by these reagents and that the product is also propane or a derivative. However, in the case of cyclopropane a halogen atom in the product is attached to a terminal carbon atom.

The cyclobutane ring is more stable than the cyclopropane ring for it is not opened under the conditions above. However, it is opened by hydrogen at high temperature when in contact with nickel The product is *n*-butane.

The Baeyer Strain Theory. In order to account for the greater reactivity of cyclopropane, compared to other cycloalkanes, Baeyer took account of the strain involved in closing the ring (1885). On the assumption that the carbon atoms in a cyclic hydrocarbon lie in a plane, the angle by which a given carbon bond must be distorted from the tetrahedral angle of 109° 28′ is assumed to be one half of the difference between the tetrahedral angle and the angle of the corresponding regular polygon. The angular distortion is given by the expression,

$$s = \frac{1}{2}[109^\circ\,28' - (180^\circ - 360^\circ/n)]$$

where s is the angle of strain and n is the number of carbon atoms in the ring. The principle can be extended to ethylene, in which only two carbon atoms are involved. In Table 29 are shown angles of strain calculated this way.

TABLE 29 | **Calculated Strain in Rings**

Ethylene	$\frac{1}{2}(109^\circ\,28'-0)$	54° 44′
Cyclopropane	$\frac{1}{2}(109^\circ\,28'-60^\circ)$	24° 44′
Cyclobutane	$\frac{1}{2}(109^\circ\,28'-90^\circ)$	9° 44′
Cyclopentane	$\frac{1}{2}(109^\circ\,28'-108^\circ)$	0° 44′
Cyclohexane	$\frac{1}{2}(109^\circ\,28'-120^\circ)$	−5° 16′ [a]
Cycloheptane	$\frac{1}{2}(109^\circ\,28'-128^\circ\,34')$	−9° 33′ [a]
Cyclooctane	$\frac{1}{2}(109^\circ\,28'-135^\circ)$	−12° 46′ [a]

[a] Strain largely relieved by nonplanar arrangement.

The cyclopropane ring has the largest amount of strain. It is not surprising, therefore, that this ring is the least stable and undergoes scission with

some reagents which add to the olefinic double bond. Also, data on heats of combustion (Table 28) indicate that the three-membered ring is the least stable ring system, for it contains more energy per methylene group (CH_2) than do the others, and also that the six-membered ring is the most stable. From Table 29 it might be inferred that the strain would increase as the number of carbon atoms is increased above five. However, it is known that the carbon atoms are not planar in the cyclohexane ring, and this factor relieves most of the strain. Large rings appear to have only slight strain on the basis of heats of combustion, where deviation from normal is small (Table 28).

Nonplanar Rings. The cyclohexane ring may assume one of two possible nonplanar arrangements, commonly known as the chair form (Fig. 8) and

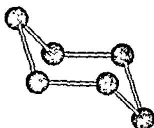


Figure 8 · Chair Form of Cyclohexane

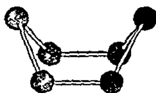


Figure 9 · Boat Form of Cyclohexane

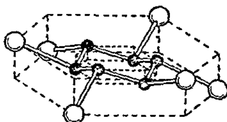
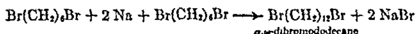


Figure 10 · Space Arrangement of the Molecule of α-Hexabromocyclohexane

the boat form (Fig. 9). In Figure 8 the carbon atoms are located alternately above and below the plane of the ring, and are commonly spoken of as staggered. This arrangement has been found in the solid compound, α-hexabromocyclohexane (α-benzene hexabromide), the structure of which has been determined by X-ray diffraction methods (Fig. 10). In the liquid or gaseous state at the ordinary temperature, cyclohexane probably is a mixture of the two forms.

Rings of seven or more carbon atoms are essentially strain free, owing to a nonplanar arrangement of the carbon atoms. However, the values in the last column of Table 28 indicate that there is a small amount of strain in the cycloheptane and cyclooctane rings.

Intramolecular vs. Intermolecular Reactions. When sodium reacts with 1,6-dibromohexane, another reaction, namely, an intermolecular reaction between two molecules of the dibromide, can take place in addition to the intramolecular ring-closure reaction.



The product is a dibromide having a normal chain of twelve carbon atoms. The intramolecular reaction of this compound is hindered by the longer chain length, owing to lowered probability of two bromine atoms in the same molecule approaching each other close enough for ring closure to take place. The intermolecular reaction also decreases with chain length, but not nearly so rapidly as the ring closure reaction. The intermolecular reaction, therefore, is the main reaction with α,ω-dibromoheptane and dibromides of higher alkanes. Once started, the long chain reaction can continue, with formation of high molecular weight compounds. As the chain gets longer, the probability of ring closure becomes progressively less. Ring closure reactions are favored by dilution with a suitable solvent.

THE PETROLEUM INDUSTRY

Occurrence. Petroleum (crude oil) and natural gas constitute the major source of hydrocarbons, and are found widely distributed throughout the world. The order of production by countries in 1950 was: United States, Venezuela, U.S.S.R., Iran, and Saudi Arabia. In the United States, which accounts for about 60 per cent of the world production of 3 billion barrels, the principal producing states are Texas, California, Louisiana, and Oklahoma.

There are three general classes of petroleum, *viz.*, (1) the paraffin-base petroleums, (2) the naphthene-base petroleums and (3) the mixed-base petroleums. The first consist mainly of paraffin hydrocarbons, the second mainly of naphthene hydrocarbons, that is, cyclopentane, cyclohexane, and their derivatives, and the third class contains large quantities of both acyclic and cyclic hydrocarbons. The first and second class are extreme types, for most petroleums contain substantial amounts of both paraffin and naphthene hydrocarbons. Petroleums that contain much brittle black asphaltic material are called asphalt-base petroleums. They belong to the group of napthene-base or mixed-base petroleums. Other components of petroleum are aromatic hydrocarbons and compounds having nitrogen, sulfur, or oxygen as a part of the molecule.

Crude oils vary markedly in color, from greenish to black, and in viscosity, from a liquid as mobile as kerosene to one so thick that it barely flows. The mobile ones are called light oils; the thick ones, heavy oils. The more mobile the crude the higher its content in hydrocarbons of the gasoline range.

The first oil well, dug in Pennsylvania in 1859, was only 69.5 feet deep. Recently petroleum production has been obtained from wells over 3 miles deep. Petroleum is such an important factor in modern life that the search for new deposits proceeds actively.

Distillation of Crude Oils. Originally and until after World War I crude oil was separated into crude fractions by distillation from oil stills in a discontinuous process, often designated straight run distillation. Fractional distillation through frac-

tionating columns is now the usual procedure because this effects a sharper separation and is carried out as a continuous process. The crude flows continuously into the column, usually into the side, various volatile fractions are taken off at different levels and the residue flows out at the bottom. The fractions are gasoline, approximate boiling range 100 to 400° F (38–204° C), kerosene, b.p. 400 to 600° F (204–315° C), and gas oil. (Another distinguishing property of these fractions is the density.) The undistilled residue usually is called fuel oil. Often separation is made into still more fractions, either during the initial distillation or subsequently. Petroleum ether is the most volatile cut, usually 40 to 60° C, but the name is applied to other cuts also, with other temperature ranges, 60 to 80°, 80 to 100°, 100 to 120° These are often called ligroin, also. A naphtha cut is sometimes made between gasoline and kerosene. Also paraffin (paraffin wax) and lubricating oils are obtained from the fuel oil portion by distillation under reduced pressure.

The various components of petroleum find extensive use. The biggest demand is for gasoline, as a motor fuel. Petroleum does not produce enough gasoline by distillation to meet the demand This has led to the development of other methods, for example, recovery of gasoline from natural gas, the pyrolysis of high molecular weight materials into lower molecular weight liquids, and the manufacture of synthetic gasoline. Kerosene is employed for lighting, to some extent. Historically it was the increasing demand for kerosene that stimulated the petroleum industry in its early days. Petroleum ether, ligroin, and naphtha are solvents for special purposes.

The gas oil fraction is so called because formerly it was an important source of illuminating gas, a mixture of methane and hydrogen, obtained by pyrolysis at 1000 to 1200° C. This gas, sometimes called reformed gas, still serves as an illuminant, but mainly as an auxiliary supply to natural gas at times of peak loads. The fuel oil residue may be used as fuel, for example in furnaces, or may, depending upon its composition, be a source of paraffin, lubricating oil, or asphalt. Usually when the asphalt content is high the components characteristic of lubricating oils are low in amount.

The principal products obtained from petroleum by distillation are petroleum ether, ligroin, gasoline, naphtha, kerosene, gas oil, paraffin, and lubricating oil; asphalt is a residium

Natural Gasoline. This is obtained from natural gas by one or more of these operations: refrigeration, absorption, and compression. Natural gas contains varying amounts of propane, the butanes, and the pentanes, and quite small amounts of higher hydrocarbons. Natural gasoline is a very volatile liquid, owing to the presence of propane and butane. The propane and butane are removed by properly controlled distillation so as to "stabilize" the product, otherwise it would be too volatile, or "wild." Natural gasoline usually is blended with a gasoline lacking lower boiling components, so as to impart volatility for aid in starting.

Propane is a liquid under sufficient pressure and is a good solvent for some purposes. It is used in one process of refining lubricating oil. The butane fraction contains the normal and the iso hydrocarbons Isobutane is especially useful in the alkylation reaction (pp. 56, 71). Butane is marketed extensively in cylinders for household use in rural areas as a fuel.

Antiknock Gasoline. With the advent of higher compression motors in the decade following World War I it became desirable to develop fuels that would burn smoothly without detonation (knocking). Of the large number of additives tested, tetraethyllead was one of the best. Also it was found that branching of the hydrocarbon chain decreased knocking and that 2,2,4-trimethyl pentane ("isooctane"), b.p. 99°,

was the best of a large number in the earlier work. Its performance was called 100, and that of *n*-heptane, b.p. 98°, a bad knocker, was called zero. An antiknock scale was developed from these two hydrocarbons. A 70 octane gasoline is one that has the same performance in a testing engine as a mixture of the two hydrocarbons having 70 per cent of "isooctane." In Table 30 are listed the octane ratings of a number of hydrocarbons.

TABLE 30 | **Octane Ratings of Hydrocarbons**[a]

NAME	FORMULA	B.P. °C	OCTANE RATING
	PARAFFINS		
n-Nonane	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	150	−45
n-Octane	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	125	−17
n-Heptane	$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	98	0
n-Hexane	$CH_3CH_2CH_2CH_2CH_2CH_3$	69	25
n-Pentane	$CH_3CH_2CH_2CH_2CH_3$	36	61
Isopentane	$CH_3CHCH_2CH_3$ CH_3	28	90
n-Butane	$CH_3CH_2CH_2CH_3$	0	92
Isobutane	CH_3CHCH_3 CH_3	− 12	99
2,2,4-Trimethyl-pentane	CH_3 $CH_3CCH_2CHCH_3$ CH_3 CH_3	99	100
Propane	$CH_3CH_2CH_3$	−44	100
	NAPTHENES		
Cyclohexane	C_6H_{12}	69	77
Cyclopentane	C_5H_{10}	36	82
	OLEFINS		
1-Heptene	$H_2C{=}CHCH_2CH_2CH_2CH_2CH_3$	93	73
1-Butene	$H_2C{=}CHCH_2CH_3$	−6	80
Propene	$H_2C{=}CHCH_3$	−47	85
	AROMATICS		
Benzene	CH—CH HC CH CH=CH	80	110
Toluene	CH—CH HC CCH_3 CH=CH	110	104

[a] E. F. Obert, *Internal Combustion Engines*, 2d ed., International Text Book Co., Scranton, Pa., 1950, pp 218, 219, 224, 225.

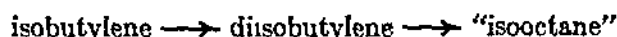
It is seen from Table 30 that any normal alkane has a higher octane number than the next higher homolog, that is, the tendency to knock increases with molecular

weight. More important, branching of the chain increases the octane number, that is, decreases the tendency to knock. Also, unsaturation increases octane number. The effect of tetraethyllead is to raise octane ratings. Values higher than 100 are now commonly realized. High octane gasoline for internal-combustion engines is especially important in aviation. The behavior of gasolines as aviation fuel is indicated in terms of a performance number, referred to "isooctane" as 100. Many have values above this figure. As jet engines come into more general use the demand for high octane gasoline may not be so pressing, because a large variety of fuels can be used in jet engines.

Cracked Gasoline. This is produced from higher boiling materials, for example, gas oil or fuel oil, but generally not if these are good sources of lubricants, by heating under pressure to various temperatures. *It is better to use a fraction called cracking* stock and comprising a distillate from fuel oil, so as to minimize coke formation by elimination of asphaltic material. In the Dubbs process the temperature is 840° F. (449° C.) and the pressure 350 pounds. The result is a mixture of gas, gasoline, fuel oil, and coke. The amounts of gasoline and fuel oil are comparable. A number of other cracking processes have been developed, and the old thermal cracking process is being displaced by other processes that give higher yields of gasoline, in particular, catalytic cracking.

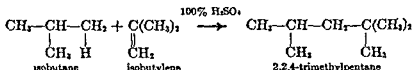
Cracked gasoline is a mixture of saturated and unsaturated hydrocarbons (p. 54). This is a desirable feature because of the higher antiknock value of unsaturated hydrocarbons. The gas also is a mixture of saturated and unsaturated hydrocarbons. Because of the complex nature of the cracking stock and the multiplicity of reactions taking place (it will be recalled that the relatively simple hydrocarbon, butane, can decompose in more than one way), the number of products formed is so large that any representation of the process by simple equations is not possible.

Synthetic Gasoline. One of the first examples of a synthetic gasoline was 2,2,4-trimethylpentane (the so-called "isooctane"), the octane that forms the basis of the octane number (Table 30), first produced commercially by a combination of polymerization and hydrogenation (p. 74).



isobutylene ⟶ diisobutylene ⟶ "isooctane"

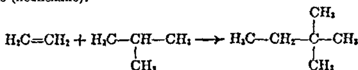
This older method has been largely supplanted by alkylation.



$$CH_3-\underset{CH_3}{CH}-\underset{H}{CH_2} + \underset{CH_2}{C}(CH_3)_2 \xrightarrow{100\%\ H_2SO_4} CH_3-\underset{CH_3}{CH}-CH_2-\underset{CH_3}{C}(CH_3)_2$$

isobutane isobutylene 2,2,4-trimethylpentane

Alkylation has been extended to other products, but other reactions take place less readily than the one written, because isobutane is the most reactive alkane and isobutylene the most reactive alkene. Alkylation has been accomplished in other ways. Hydrogen fluoride is a better catalyst than 100 per cent sulfuric acid. Thermal alkylation is accomplished at high pressures and high temperatures (around 500° C.). Even ethylene will then react. For example, ethylene and isobutane give 2,2-dimethylbutane (neohexane).



$$H_2C{=}CH_2 + H_3C-\underset{CH_3}{CH}-CH_3 \longrightarrow H_3C-CH_2-\overset{CH_3}{\underset{CH_3}{C}}-CH_3$$

It is evident that isobutane is much more valuable than normal butane in the alkylation process, not only because it is more reactive but also because the product is more highly branched. Just as in the case of normal pentane and isopentane, which isomerize to each other in contact with anhydrous aluminum chloride (p. 56), the butanes in the liquid state and when heated somewhat, isomerize to a mixture of the two. The components can be separated from each other by distillation.

Another source of synthetic gasoline is the Fischer-Tropsch process, developed in Germany in the decade following World War I. In this, carbon monoxide and hydrogen react at high temperatures (400–475° C.) and high pressures (200–300 atmospheres) and in the presence of a catalyst, usually iron and potassium carbonate. The product is a complex mixture of hydrocarbons and oxygenated compounds. The hydrocarbons are paraffins (normal and branched-chain) and olefins, the oxygenated compounds are alcohols, aldehydes, ketones, and acids. The proportion of various products can be altered by changing the ratio of reactants, the experimental conditions, and the nature of the catalyst. Other metals have been used in place of iron. Originally the gasoline produced had a low octane rating but newer developments give a product of 80 or better octane rating.

Catalytic Cracking. Prior to World War II it was found that cracking in the presence of special catalysts, usually aluminum silicate or aluminum magnesium silicate, gives highly branched hydrocarbons, and thus a good grade of aviation gasoline. The process received enormous impetus during the War. A typical "cat" cracking plant stands about 250 ft. high and costs about fourteen million dollars. In this the vaporized cracking stock (gas oil) at a temperature of 700 to 1000° F., meets the catalyst, either as a powder or as pellets. The catalyst is regenerated after one cycle by removal of deposited carbon through combustion. The gases produced are utilized in the alkylation process.

Changing Trends in the Petroleum Industry. In the period from the discovery of petroleum to the turn of the century kerosene was the most important product, paraffin and lubricating oils were next. Later, especially following World War I, gasoline became the most important and still is, with kerosene taking a minor role. The trend over the years has been to gasoline of higher octane ratings.

Utilization of petroleum for chemical processes increased markedly after World War I and received enormous impetus during World War II. It is increasing all of the time. Because of this trend there is an expanding demand for gaseous products, in particular lower olefins and dienes, for example isobutylene, for butyl rubber (p. 92), and 1,3-butadiene for GR rubber (p. 93).

PROBLEMS

1. From data on heats of combustion calculate, for the theoretical gas phase reaction, ΔH of hydrogenation of:

   a) cyclopropane to propane
   b) cyclobutane to butane
   c) cyclopentane to pentane
   d) cyclohexane to hexane
   e) cycloheptane to heptane

2. Indicate by name or structural formula the theoretically possible, structurally isomeric monobromo derivatives of:

a) methylcyclopentane
b) methylcyclohexane
c) ethylcyclopentane
d) dimethylcyclobutanes
e) dimethylcyclopentanes
f) dimethylcyclohexanes
g) trimethylcyclopropanes
h) trimethylcyclobutanes
i) trimethylcyclopentanes
j) methylethylcyclobutanes

3. Indicate by name or formula the theoretically possible, structurally isomeric dibromo derivatives of:

a) methylcyclopropane
b) methylcyclobutane
c) ethylcyclobutane
d) methylcyclopentane
e) ethylcyclopentane
f) methylcyclohexane
g) ethylcyclohexane
h) dimethylcyclopropanes
i) dimethylcyclobutanes
j) dimethylcyclopentanes
k) dimethylcyclohexanes
l) trimethylcyclopropanes

CHAPTER 8

Halogen Derivatives of Aliphatic Hydrocarbons

From a chemical point of view it is desirable to differentiate the monohalogen compounds, or alkyl halides, from the polyhalogen compounds.

ALKYL HALIDES

These are monohalogen derivatives of the paraffin hydrocarbons and conform to the general formula, $C_nH_{2n+1}X$. Thus they may be regarded as derivatives of the paraffin hydrocarbons, C_nH_{2n+2}, by the replacement of one hydrogen atom by a halogen atom The halogen atom is thus a functional group, and is capable of being replaced by other functional groups, as for example the hydroxyl group in alcohols Also, alkyl halides may be regarded as derived from the hydrogen halides, HX, by the replacement of the hydrogen atom by an alkyl radical. In some chemical reactions the alkyl halides resemble the hydrocarbons, in others, the hydrogen halides.

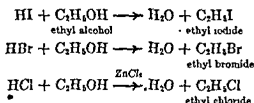
Preparation of Alkyl Halides. Alkyl chlorides and bromides may be obtained by direct halogenation of paraffin hydrocarbons. Iodine does not react, and fluorine is so excessively reactive that usually the hydrocarbon is decomposed. Carbon tetrafluoride and carbon are formed. Direct substitution *with chlorine or bromine usually is not practical for the laboratory preparation* of pure alkyl halides because: (1) the paraffins often are not pure, but are contaminated by homologs or isomers; (2) hydrocarbons above ethane usually yield mixtures of alkyl halides; (3) the alkyl halides also undergo substitution leading to the formation of dihalogenated and other products; (4) control of conditions during some halogenations (especially chlorinations) often is difficult.

In industry many alkyl chlorides and higher chlorinated compounds are obtained by direct chlorination of alkanes, especially of methane, ethane, propane, butanes, and pentanes. Sometimes the reactants are passed through hot reaction zones, at temperatures as high as 400 or 500°. At these temperatures higher alkyl halides decompose to yield olefins. Sometimes the reaction is aided by light of short wave length, and then is carried out at much lower temperatures, even at room temperature. At the lower temperatures (below 100°) the relative rates of formation of different types are in the

order, tertiary > secondary > primary. At high temperatures the rates are more alike. Sometimes catalysts are present, for example, chlorides of aluminum, iron, copper, or other metals. These usually favor the formation of dichloro and higher products. Methyl chloride is obtained by passing a mixture of methane and chlorine, with the methane in large excess, through a reaction zone at 300 to 400°. Some methylene chloride, CH_2Cl_2, is formed also. When chlorine is in excess, the main product is carbon tetrachloride; when in an approximately equimolar ratio, the reaction product is a mixture.

Pure alkyl halides are prepared conveniently in the laboratory from the monohydric alcohols, $C_nH_{2n+1}OH$ (Chap. 10) by the action of hydrogen halides (anhydrous or concentrated aqueous solution) or of inorganic acid halides, *especially the phosphorus halides. In these reactions the hydroxyl group of* the alcohol is replaced by a halogen atom.

1. *Alcohols and hydrogen halides.*



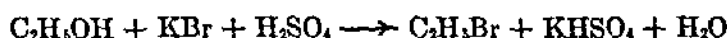
$$\underset{\text{ethyl alcohol}}{HI + C_2H_5OH} \longrightarrow H_2O + \underset{\text{ethyl iodide}}{C_2H_5I}$$

$$HBr + C_2H_5OH \longrightarrow H_2O + \underset{\text{ethyl bromide}}{C_2H_5Br}$$

$$HCl + C_2H_5OH \xrightarrow{ZnCl_2} H_2O + \underset{\text{ethyl chloride}}{C_2H_5Cl}$$

The reaction may be carried out by passing the anhydrous hydrogen halide into the alcohol, but usually the alcohol is heated with a concentrated aqueous solution of the acid. The relative rates are: HI > HBr > HCl; and tertiary alcohol > secondary alcohol > primary alcohol. The iodides and bromides usually can be distilled over as they are formed. Zinc chloride (anhydrous) usually is added to increase the rate of hydrochloric acid with primary and secondary alcohols, and sometimes sulfuric acid is added to increase the rate of hydrobromic acid with primary alcohols. The reaction of an alcohol with an alkyl halide is reversible. The principles involved in the reaction are amplified under Alcohols, Chapter 10.

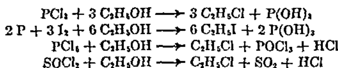
2. *Alcohols, an inorganic bromide, sulfuric acid, and water.*



$$C_2H_5OH + KBr + H_2SO_4 \longrightarrow C_2H_5Br + KHSO_4 + H_2O$$

This combination is a modification of the method mentioned in the preceding paragraph, and is much used for the preparation of primary bromides, mainly because of convenience and economy. The corresponding reaction with potassium chloride or potassium iodide is not satisfactory, the former because primary alcohols react too slowly, the latter because sulfuric acid oxidizes iodide ion to iodine.

3. *Alcohols and acid halides* (phosphorus trichloride, phosphorus tribromide, phosphorus and iodine, phosphorus pentachloride, thionyl chloride, etc.).



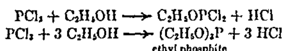
$$PCl_3 + 3\,C_2H_5OH \longrightarrow 3\,C_2H_5Cl + P(OH)_3$$

$$2\,P + 3\,I_2 + 6\,C_2H_5OH \longrightarrow 6\,C_2H_5I + 2\,P(OH)_3$$

$$PCl_5 + C_2H_5OH \longrightarrow C_2H_5Cl + POCl_3 + HCl$$

$$SOCl_2 + C_2H_5OH \longrightarrow C_2H_5Cl + SO_2 + HCl$$

These reactions proceed more rapidly than in the case of the hydrohalic acids, sometimes with almost explosive violence. Other reactions also may take place, producing mixed ester chlorides and finally the organic esters of the inorganic acids. This is especially true of phosphorus trichloride, which yields a chlorophosphite ester and even a trialkyl ester of phosphorous acid.



$$PCl_3 + C_2H_5OH \longrightarrow C_2H_5OPCl_2 + HCl$$
$$PCl_3 + 3\ C_2H_5OH \longrightarrow \underset{\text{ethyl phosphite}}{(C_2H_5O)_3P} + 3\ HCl$$

Iodine and phosphorus constitute the best reagent for alkyl iodides, thionyl chloride (with a tertiary amine such as pyridine), for alkyl chlorides.

4. *Olefins and hydrogen halides.*



$$HBr + CH_2{=}CHCH_2CH_2CH_3 \longrightarrow CH_3CHBrCH_2CH_2CH_3$$

Reasonably pure 2-bromoalkanes may be obtained from 1-alkenes. However the method is relatively unimportant (see Chap. 5).

Physical Properties of Alkyl Halides. In Table 31 are listed some of the lower normal alkyl halides, with boiling points and specific gravities. The lower alkyl halides are either gases (methyl chloride, methyl bromide, and ethyl chloride) or liquids insoluble in water and in concentrated sulfuric acid,

TABLE 31 | Constants of Some Normal Alkyl Halides

RADICAL IN COMBINATION WITH HALOGEN	CHLORIDE		BROMIDE		IODIDE	
	boiling point °C	specific gravity 20°/4°	boiling point °C	specific gravity 20°/4°	boiling point °C	specific gravity 20°/4°
Methyl	−23.7	0.920	4.6	1.732 [a]	42.6	2.279
Ethyl	12.5	0.910	38.4	1.440	72.2	1.933
Propyl	46.6	0.890	71.0	1.335	102.4	1.747
Butyl	78.5	0.884	101.6	1.276	130	1.617
Amyl	108.3	0.883	129.7	1.223	157	1.517
Hexyl	134	0.882	156	1.173	180	1.441
Heptyl	159.5	0.881 [b]	180	1.133 [b]	203.8	1.401
Octyl	184.6	0.879	202	1.116 [b]	225.5	1.341 [c]

[a] At 0°. [b] At 16°. [c] At 14.5°.

soluble in common organic solvents. The liquid chlorides are lighter than water; the bromides and iodides are heavier. The boiling point increases as the size of the molecule increases, while the density decreases. This latter is due to the fact that the influence of the halogen atom, which gives weight to the molecule, diminishes as the number of carbon atoms increases. Alkyl halides are colorless, but the iodides decompose slowly (more rapidly when exposed to light) with the liberation of free iodine, which is soluble in the liquid and imparts to it a brown color.

The physical properties of isomeric alkyl halides are often quite different; as shown in Table 32. Branching of the carbon chain or moving the halogen atom away from the end of the carbon chain causes a lowering of boiling point and specific gravity.

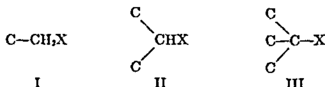
TABLE 32 | **Some Physical Constants of Propyl and Butyl Halides**

RADICAL IN COMBINATION WITH HALOGEN	CHLORIDE		BROMIDE		IODIDE	
	b.p. ° C	sp. gr.	b.p. ° C	sp. gr.	b.p. ° C	sp. gr.
$CH_3CH_2CH_2$ (normal propyl)	46.6	0.890	71.0	1.335	102.4	1.747
$(CH_3)_2CH$ (isopropyl)	36.5	.859	60	1.310	89.5	1.705
$CH_3CH_2CH_2CH_2$ (normal butyl)	78.5	.884	101.6	1.276	130	1.617
[illegible]	68.9	.875	91.4	1.261	120.4	1.605
[illegible]	68.2	.871	91.3	1.251 [a]	119	1.596
[illegible]	50.7	.840	73.3	1.222	100	1.571 [b]

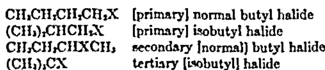
[a] At 25°. [b] At 0°.

The dipole moment of an alkyl halide is an important property because of its connection with chemical reactivity. The values are: for methyl chloride, 1.86 D; for methyl bromide, 1.79 D; and for methyl iodide, 1.62 D. The values for higher homologs are close to those of the methyl compounds. It will be recalled that paraffin hydrocarbons have zero dipole moment (Table 11, p. 28). (Compare with n-hexane, Tables 11 and 13.)

Nomenclature. There are three classes of alkyl halides; **primary,** in which the halogen atom is joined to a primary carbon atom; **secondary,** in which it is joined to a secondary carbon atom; and **tertiary,** in which it is joined to a tertiary carbon atom. The characteristic structures of these three types are shown by I, II, and III, respectively.

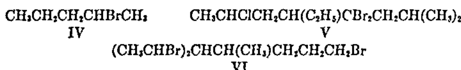


The trivial names of the butyl halides are derived from a combination of the names of the three classes with the names of the two hydrocarbons, normal and iso, as indicated below, omitting the bracketed expressions.



There are eight pentyl (amyl) bromides. To name them all in this manner is not practical, since this means eight prefixes, one for each isomer.

The I.U.C. system is much simpler. In this, the longest chain containing the halogen atom is selected and named. The position of the substituent is indicated in the usual manner, so as to give the halogen atom the smaller number. Thus IV is 2-bromopentane, not 4-bromopentane. In case there are side chains, the hydrocarbon is named first, giving the side chains the lower numbers; then the positions of the halogen atoms are indicated. Thus V is 7-chloro-4,4-dibromo-2-methyl-5-ethyloctane. In case a halogen atom is located on a side chain, the position is indicated by numbering the carbon atoms of the side chain, starting next to the main carbon chain, and retaining the name of the alkyl radical. Thus VI is 2,7-dibromo-3-(1-bromoethyl)-4-methylheptane.



$$CH_3CH_2CH_2CHBrCH_3 \quad \text{IV}$$

$$CH_3CHClCH_2CH(C_2H_5)CBr_2CH_2CH(CH_3)_2 \quad \text{V}$$

$$(CH_3CHBr)_2CHCH(CH_3)CH_2CH_2CH_2Br \quad \text{VI}$$

Reactions of Alkyl Halides. These may be divided into two groups: *first, those characteristic of the alkyl radical; and second, those due to the* halogen atom. The characteristic reactions of the alkyl radical are those of saturated hydrocarbons, *viz.*, substitution and oxidation. Alkyl halides when treated with chlorine or bromine under the proper conditions of temperature and illumination undergo further substitution. For example, 1-chloro and 2-chloropropane can be chlorinated to dichloropropanes, the former yielding a mixture of three isomeric dichlorides and the latter, two. There is some difference in the rates of the different reactions; the presence of chlorine tends to cut down the reactivity of the hydrogen atom joined to the same carbon, while hydrogen on a secondary carbon atom is more reactive than one on a primary. Alkyl halides will burn in oxygen. Accumulation of halogen, however, decreases the ability to combine with oxygen, and carbon tetrachloride, in which all hydrogen atoms are replaced by chlorine, not only will not burn but prevents other substances from burning.

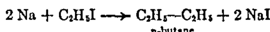
The principal reactions of alkyl halides are those involving the halogen atom. These are reactions with metals, salts, ammonia, water, hydriodic acid, and strong bases. The reactions with metals, especially the strongly metallic ones, are markedly exothermic.

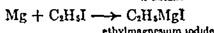
1. *Metals.* In the presence of water or other solvent able to supply hydrogen, for example, an alcohol or an acid, the halogen atom can be replaced by hydrogen (reduction of the alkyl halide)

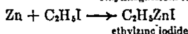


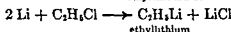
$$2\,C_2H_5I + 2\,Zn + H_2SO_4 \longrightarrow 2\,C_2H_6 + ZnI_2 + ZnSO_4$$

In the absence of such compounds, metals act differently. Sodium effects the Wurtz coupling (Chap. 4), magnesium (plus ether) and zinc form addition compounds, lithium forms an alkyllithium (Chap. 9).



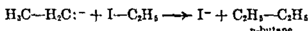


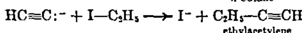


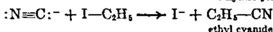


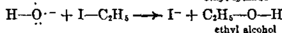
These organometallic compounds are much employed in synthesis (Chap. 9).

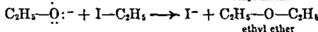
2. *Salts.* Sodium and potassium salts of weak acids react by replacing the halide atom with a negative radical. The reaction usually is carried out in a mixed solvent like aqueous alcohol, to obtain solution of both the alkyl halide and the salt, but not if the solvent reacts with the salt (*i.e.*, alkynides). Usually heating is necessary, owing to slowness of the reaction. The equations below represent reactions of ethyl iodide with ethyllithium, sodium acetylide, sodium cyanide, sodium hydroxide, sodium ethoxide, sodium hydrosulfide, sodium mercaptide, and sodium acetate, respectively. Sodium hydroxide may be regarded as the sodium salt of the weak acid, water.

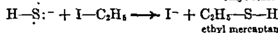


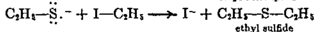


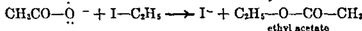




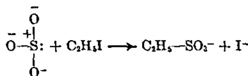


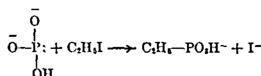




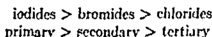


However, sodium sulfite and sodium phosphite react in a manner not expected, yielding as the initial products, sodium ethanesulfonate, $CH_3CH_2—SO_3Na$, and sodium ethanephosphonate, $CH_3CH_2—PO_3HNa$, respectively.





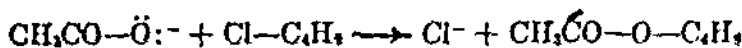
Two of the reactions, *viz.*, those with sodium acetylide and sodium cyanide, are important in synthesis as means of lengthening a carbon chain. Relative rates in this type of reaction are in the orders:



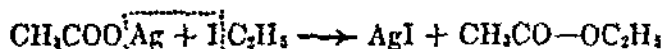
iodides > bromides > chlorides
primary > secondary > tertiary

Fluorides are so unreactive they need not be considered.

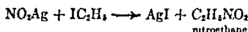
The reaction of salts of organic acids, mainly acetates, with alkyl chlorides obtained by the chlorination of paraffin hydrocarbons, is important industrially in the manufacture of esters such as butyl and amyl acetate.

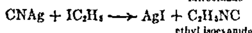


Silver salts in general undergo similar reactions. Often they react more rapidly than do sodium or potassium salts, but insoluble salts such as silver sulfide may not react. Even silver salts of strong acids may react with alkyl iodides. Relative rates are in the order: tertiary > secondary > primary.

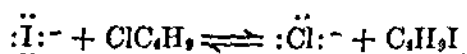


Silver nitrite and silver cyanide react abnormally, giving mainly nitroalkanes and alkyl isocyanides, respectively, along with some of the normal products.



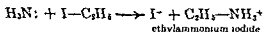


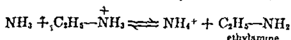
Alkyl chlorides (bromides less readily) react with potassium iodide (best in anhydrous acetone) to form the corresponding alkyl iodide.



The reaction is reversible: the equilibrium, which favors the alkyl iodide, is disturbed by crystallization of the less soluble inorganic chloride. The addition of potassium iodide usually accelerates the rate with which an alkyl chloride reacts, owing to the conversion of the chloride to the iodide first.

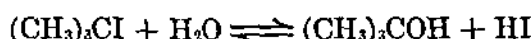
3. *Ammonia.* The halogen atom is replaced by the amino radical, NH_2, producing an amine.





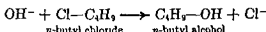
4. *Water.* An alkyl halide undergoes slow hydrolysis to the alcohol when heated with water, a reversal of the preparation reaction (see Chap. 10 for more detail). Relative reactivities are in the orders: tertiary > secondary >

primary; and iodides > bromides > chlorides. Tertiary butyl iodide undergoes extensive hydrolysis in warm water.



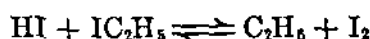
Higher primary chlorides react only very slowly with water, even at 200°.

The hydrolysis of primary alkyl halides proceeds more rapidly when a base is present, for hydroxide ion reacts more rapidly than does water.



The hydrolysis of alkyl chlorides under basic conditions at elevated temperatures, usually above 150°, is important industrially in the manufacture of alcohols, especially methyl, butyl, and pentyl alcohols, from paraffin hydrocarbons. A side reaction is unsaturation, which often is the principal reaction with tertiary halides, sometimes with secondary.

5. *Hydriodic acid and phosphorus* An alkyl iodide when heated to a sufficiently high temperature (usually under pressure) is partly reduced to the hydrocarbon



Phosphorus is added to reduce iodine to hydriodic acid and thus allow the reaction to proceed to completion.



This reduction method was much used formerly. It has been superseded largely by the Grignard method (Chap. 9).

6. *Strong bases.* When an alkyl halide is heated with a strong base, preferably under anhydrous conditions, dehydrohalogenation is effected (Chap. 5).



Sometimes the operation is carried out in a solvent that dissolves both reactants. Ethyl alcohol has been much used; dihydroxyethylether, $HOCH_2CH_2OCH_2CH_2OH$, has the advantage of a much higher boiling point. With lower alcohols a side reaction is the formation of an ether. The reaction is described more fully under Dehydrohalogenation (p. 114).

The Displacement Reaction. The replacement of one negative radical by another, as in the reactions of ethyl iodide above with sodium and potassium salts, is often called displacement or substitution. It is essentially the expulsion of the radical as a negative ion by a second negative ion. Tertiary halides usually are converted to unsaturated hydrocarbons by the reagent; secondary halides often undergo unsaturation as well as conversion to the desired product. Primary halides usually give good yields in the replacement reaction.

The fastest reacting salts (sodium and potassium) are those of the weakest acids. The weaker the acid, the more strongly nucleophilic is the negative ion of the corresponding salt.

There is a formal resemblance between the reactions of hydrogen iodide and ethyl iodide with alkali salts of weak acids or silver salts of most acids. However, hydrogen iodide reacts much more rapidly than ethyl iodide. This is due to the fact that hydrogen iodide in the proper medium ionizes readily to positive hydrogen and negative iodide ions, but ethyl iodide is so weakly ionized that the effect cannot be demonstrated by conductivity methods. Thus a reaction of hydrogen iodide involves merely an exchange of ions without the necessity of bond breaking, whereas a reaction of ethyl iodide involves the release of the electron pair of the carbon-to-iodine bond by the carbon atom, before the iodine atom can leave the molecule as iodide ion.

The initiation of reaction between an alkali salt and ethyl iodide involves close approach of the negative ion. It is attracted to the carbon nucleus by virtue of its unshared electrons. It attacks the carbon atom on the side opposite to the iodine atom, owing to the influence of the dipole of the carbon-to-iodine bond, the positive end of which is the carbon atom, the negative end the iodine atom (Table 15, p. 33). As the new bond strengthens, the bond to the iodine atom weakens until finally the iodide ion is expelled and the new molecule is formed. The way this takes place in the reaction of hydroxide ion with an alkyl iodide is indicated by VII, VIII, and IX in Figure 11, VII and IX being the initial and final states respectively, and VIII an unstable intermediate or the so-called transition state.

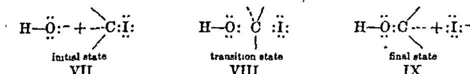


Figure 11 • The Umbrella Effect in Displacement Reactions

In VIII the original tetrahedral arrangement of three of the bonds about the central carbon atom has changed to a planar arrangement: the two bonds involved in the change are of equal strength but weaker than the other three bonds.

The reaction actually is a displacement of the iodine atom, rather than a simple replacement, for the entering radical or ion in IX is attached to the carbon atom at a position different from the one occupied by the iodine atom in VII. Evidence for this point of view is presented later under Optical Inversion (Chap. 18). This mechanism of the displacement reaction sometimes is referred to as the umbrella effect, since the change resembles an umbrella being turned inside out.

This picture of the mechanism accounts satisfactorily for relative rates, *viz.*, the most strongly nucleophilic reagents are in general the most reactive types of salts, and iodides are the most reactive of the alkyl halides. In the first step, which is the formation of the intermediate addition complex, attraction between reactants would presumably be stronger, the more strongly nucleophilic the reagent. In the second step, which is the expulsion of the halogen atom as halide ion, the driving force of the overall exchange reaction

would depend in part upon the difference in the bond energies of the bond formed and that of the bond broken. Thus for a given electrophilic reagent, $-\Delta H$ would decrease in the order RI > RBr > RCl, since bond energies are, for C—I, 45.5 kcal., C—Br, 54.0 kcal., and C—Cl, 66.5 kcal.

The mechanism by which silver salts and other similar (mercury) salts react is different, since many of these are weakly ionized. Silver (also mercuric) ion is known to form coordination complexes with halide ions, for example, $AgCl_2^-$. It is believed that the first step in the reaction of a silver salt with an alkyl halide is coordination with the halogen atom forming an unstable addition compound. Then this decomposes to give silver halide and a new organic compound.

The reaction of sulfite ion and phosphite ion with alkyl halides is also understandable. In these cases the carbon atom becomes attached preferably to sulfur or phosphorus rather than to oxygen.

S_N1 and S_N2 Mechanisms. For primary alkyl halides the idea of an intermediate complex involving both reactants is supported by the observation that the rate is second order, that is, first order with respect to the alkyl halide, and first order also with respect to the other reactant. The English group of organic chemists, in particular, Ingold, designate these as substitution reactions, and assign them to the S_N2 type, S for substitution, N for nucleophilic, and 2 for second order.

The reaction of tertiary butyl chloride (and other tertiary halides) with sodium hydroxide in aqueous alcoholic solution is first order, for it is independent of the hydroxide ion concentration and first order with respect to the halide concentration. Such a reaction is called S_N1. According to some workers it is thought to involve ionization to give a very reactive carbonium ion, $(CH_3)_3C^+$; others believe that the reaction is essentially one of solvolysis.

Secondary alkyl halides may react by either or both mechanisms, depending upon the halogen atom of the halide, the nature of the other reactant, and the conditions, particularly the solvent. The rate of reaction by the S_N1 mechanism is in the order, *tert* > *sec* > *prim*, and that by the S_N2 mechanism, *prim* > *sec* > *tert*.

Dehydrohalogenation. Alkyl halides decompose into an alkene and hydrogen halide when heated sufficiently. The relative tendencies to undergo this reaction are in the order: tertiary > secondary > primary. Tertiary halides sometimes are so unstable that distillation at atmospheric pressure is accompanied by decomposition, as for example, tertiary butyl iodide.



$$(CH_3)_3CI \longrightarrow (CH_3)_2C{=}CH_2 + HI$$

The reaction is the reversal of the addition reaction.

From Table 25, page 68, it is evident that a gas phase decomposition of an alkyl halide to an olefin and hydrogen halide, if it could take place at room temperature would be endothermic as follows: 9.7 kcal. for chlorides, 12.6 kcal. for bromides, and 20 kcal. for iodides. Thus gas phase dehydrohalogenation would not be expected to be significant until fairly high temperatures are

reached, 200° or higher. However, in contact with potassium hydroxide or other strong base the overall reaction is exothermic, owing to reaction between the hydrogen halide and potassium hydroxide. For example, $-\Delta H$ for the reaction of anhydrous hydrogen chloride with anhydrous potassium hydroxide is 42 kcal. above 100° (gaseous), but $-\Delta H$ is only 15 kcal. in dilute aqueous solution. The values for hydrogen bromide and iodide are similar. These data explain the much lower tendency of bases to cause dehydrohalogenation in dilute aqueous solution.

Uses of Alkyl Halides. *Alkyl halides, especially bromides and iodides,* are used extensively in organic chemistry research for synthesis of other organic compounds. On an industrial scale alkyl chlorides are important in the manufacture of other organic compounds, especially alcohols and esters. Ethyl chloride is used in the manufacture of tetraethyl lead (Chap. 9). Methyl and ethyl chlorides are useful refrigerants but are inferior to difluorodichloromethane and other polyfluorine compounds.

UNSATURATED HALOGEN COMPOUNDS

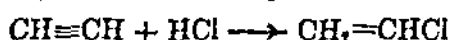
Unsaturated halogen compounds may be prepared by methods similar to those already mentioned for olefins or for saturated halides.

1. *Dehydrohalogenation of dihaloalkanes.*



$$CH_2BrCH_2Br + KOH \longrightarrow CH_2{=}CHBr + KBr + H_2O$$

2. *Addition of hydrogen halides to alkynes.*



$$CH{\equiv}CH + HCl \longrightarrow CH_2{=}CHCl$$

3. *Reaction of allyl alcohol with hydrohalic acids.*



$$CH_2{=}CHCH_2OH + HBr \longrightarrow CH_2{=}CHCH_2Br + H_2O$$

4. *High temperature chlorination of alkenes* (see p. 72).

TABLE 33 | Some Unsaturated Halogen Compounds

I.U.C. NAME	FORMULA	NAME OF RADICAL	BOILING POINTS		
			chloride °C	bromide °C	iodide °C
Haloethene [a]	$CH_2{=}CHX$	Vinyl	−13.9	15 8	56
1-Halopropene-*cis*	$CHX{=}CHCH_3$	*cis*-Propenyl	32 8	60	
1-Halopropene-*trans*	$CHX{=}CHCH_3$	*trans*-Propenyl	37 4	63.3	
2-Halopropene	$CH_2{=}CXCH_3$	Isopropenyl	22 6	48.4	
3-Halopropene	$CH_2{=}CHCH_2X$	Allyl	44.6	71.3	103
1-Halo-2-butene	$CH_3CH{=}CHCH_2X$	Crotyl	84	107 [b, c]	132
3-Halo-1-butene	$CH_3CHXCH{=}CH_2$	Methylvinylcarbinyl	64	86 5 [d]	
3-Halopropyne	$CH{\equiv}CCH_2X$	Propargyl	65	88–90	115

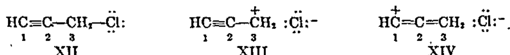
[a] This signifies chloroethene, bromoethene, or iodoethene.
[b] Isomerizes. [c] 49° at 93 mm. [d] 31° at 93 mm.

Unsaturated halogen compounds resemble alkyl halides as regards physical properties such as boiling point, specific gravity, and solubility, except that vinyl halides are more volatile than ethyl halides.

Unsaturated halogen compounds may differ markedly from alkyl halides in reactivity. Dehydrohalogenation with formation of a triple bond usually is more difficult than when a double bond is involved. In hydrolysis and replacement reactions it is well to distinguish two important types, *viz.*, **vinyl type compounds**, in which the halogen atom is attached to an unsaturated carbon atom as in vinyl chloride, $CH_2{=}CHCl$; and **allyl type compounds**, in which the halogen atom is attached to a carbon atom adjacent to an unsaturated carbon atom, as in allyl chloride, $CH_2{=}CHCH_2Cl$. In general, viny-type halides are unreactive, while allyl type halides are more reactive than the corresponding alkyl halides. However, vinyl halides undergo unsaturation and addition, and polymerize readily.

The possibility of resonance accounts for the difference in reactivity. Structural determinations by means of electron diffraction have shown that in vinyl chloride, $CH_2{=}CHCl$, the carbon-to-chlorine separation is 1.73 Å., and in propargyl chloride, $HC{\equiv}C{-}CH_2Cl$, it is 1.82 Å. The normal single-bond covalent value is 1.76 Å (see Table 5, p. 14). The data are interpreted as indicating that in vinyl chloride the bond possesses some double-bond character while in propargyl chloride it possesses some ionic character.





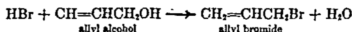
In vinyl chloride there is resonance between the normal form, X, and the excited form, XI. In the latter the chlorine atom carries a formal positive charge. In propargyl chloride there is resonance between the normal form, XII, and two ionic forms, XIII and XIV. In XIII and XIV the chlorine atom carries a formal negative charge. Additional evidence for the contribution of XIV is the separation distance between C–2 and C–3, *viz.*, 1.48 Å. This is less than the normal covalent single-bond distance of 1.54 Å., and indicates that this bond possesses some double-bond character. Compared to an alkyl chloride the chlorine atom of vinyl chloride is less easily displaced by a negative ion, owing to the contribution of XI, while the chlorine atom of propargyl chloride is more easily displaced, because of the contributions of XIII and XIV to the overall structure.

Vinyl Chloride, $CH_2{=}CHCl$. This is the most important of the unsaturated halogen compounds. It is prepared in large quantities by the reaction of hydrogen chloride with acetylene over a catalyst (p. 83), from ethylene chloride (p. 115), and directly from ethane by high temperature chlorination (400–500°). It polymerizes

readily. It does not undergo replacement (displacement) reactions. In addition reactions with hydrogen bromide it usually undergoes the abnormal reaction, yielding 1-chloro-2-bromoethane, unless oxygen is carefully excluded. It is more susceptible to the influence of oxygen in addition reactions than are olefins.

The polymerization of vinyl chloride is promoted by peroxides, recalling that of butadiene, isoprene, and chloroprene (Chap. 6). The product, polyvinyl chloride, is water repellent and flame resistant. It replaces rubber for many purposes. A trade name is Koroseal.

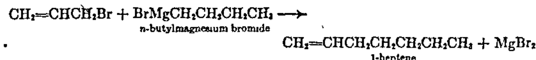
Allyl Halides, $CH_2{=}CHCH_2X$. Allyl chloride, bromide, and iodide are prepared readily from allyl alcohol by the action of the corresponding hydrohalic acid.



$$HBr + \underset{\text{allyl alcohol}}{CH{=}CHCH_2OH} \longrightarrow \underset{\text{allyl bromide}}{CH_2{=}CHCH_2Br} + H_2O$$

Allyl chloride is produced industrially by the high temperature chlorination of propylene (p. 72). Allyl iodide may be obtained also from glycerol by the action of hydriodic acid or of phosphorus and iodine (see glycerol, Chap. 11)

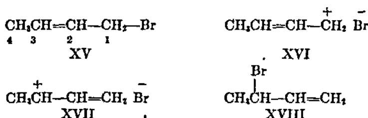
Allyl halides undergo the typical replacement reactions of ethyl iodide (p. 110) and are much more reactive than the corresponding saturated halides. They even react readily with Grignard reagents to yield 1-alkenes. The formation of 1-heptene from allyl bromide and *n*-butylmagnesium bromide is typical.



$$CH_2{=}CHCH_2Br + \underset{\text{n-butylmagnesium bromide}}{BrMgCH_2CH_2CH_2CH_3} \longrightarrow \underset{\text{1-heptene}}{CH_2{=}CHCH_2CH_2CH_2CH_2CH_3} + MgBr_2$$

The high reactivity of allyl halides can be ascribed to the fact that the carbon-to-halogen bond possesses more ionic character than a similar bond in a saturated compound because of resonance involving ionic structures, as in the case of propargyl chloride. However, the effect on bond distance is so slight that it cannot be demonstrated by measurement of bond distances.

Crotyl Bromide, $CH_3CH{=}CHCH_2Br$, and Methylvinylcarbinyl Bromide, $CH_3CBrCH{=}CH_2$. These isomeric bromides resemble allyl bromide in reactivity. However, reaction products usually are mixtures. Each bromide changes slowly at room temperature to the isomer. The isomerization is accelerated by many substances, for example, zinc chloride and aluminum chloride. The bromides can be obtained pure by fractional distillation at room temperature under reduced pressure, but distillation at atmospheric pressure yields a mixture. The isomerization is connected with resonance, which resembles that of allyl halides and propargyl chloride (XII, XIII, and XIV, p. 116). The three resonance forms of crotyl bromide are XV, XVI, and XVII.



$$\underset{\text{XV}}{\overset{4}{C}H_3\overset{3}{C}H{=}\overset{2}{C}H{-}\overset{1}{C}H_2{-}Br} \qquad \underset{\text{XVI}}{CH_3CH{=}CH{-}\overset{+}{C}H_2\ \overset{-}{Br}}$$

$$\underset{\text{XVII}}{CH_3\overset{+}{C}H{-}CH{=}CH_2\ \overset{-}{Br}} \qquad \underset{\text{XVIII}}{CH_3CH(Br){-}CH{=}CH_2}$$

Although the contributions of XVI and XVII to the overall structure are small, the presence of a positive charge on carbon atom C-3, due to the contribution of XVII,

facilitates isomerization by attracting the negatively charged bromine atom. The result of the change is methylvinylcarbinyl bromide, XVIII.

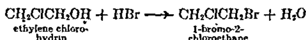
POLYHALOGEN COMPOUNDS

The principal polyhalogen compounds are those containing fluorine, important as refrigerants, and those containing chlorine, important as solvents. Fluorine compounds usually are prepared by heating halogen compounds with antimony trifluoride or mercuric fluoride. Carbon tetrachloride is easily converted to dichloridifluoromethane (p. 121).

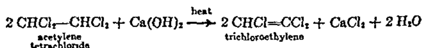
Some di- and polychloro compounds are by-products in the manufacture of alkyl chlorides by the chlorination of alkanes by flow methods through reaction vessels at elevated temperatures. These are formed as a result of two types of subsequent reaction, *viz.*, (1) a second substitution reaction and (2) unsaturation, followed by addition. By increasing the ratio of chlorine to alkane, higher chlorinated compounds are the main products. Methane can be converted mainly to carbon tetrachloride, CCl_4, with 3.3 moles of chlorine, at a temperature of 440°. To prevent flame combustion at this high temperature the chlorine is made to enter the reaction zone through a number of fine openings and at high velocity. Methane homologs can be chlorinated to yield a variety of products, depending upon molal ratios of chlorine to hydrocarbon and upon other conditions. When homologs of methyl chloride undergo dichlorination, the chlorine atom already present cuts down subsequent substitution. The effect is greatest at the attached carbon atom and drops off with the distance away. It is negligible at the third and further removed carbon atoms. Multiple substitution at a single carbon atom becomes progressively more difficult. Ethane and propane can be chlorinated completely to hexachloroethane and octachloropropane, respectively, but when vigorous chlorination of higher hydrocarbons is attempted, decomposition to simpler compounds results.

Other methods are applicable to the preparation of fluorine, chlorine, bromine, and iodine compounds.

1. *Addition of halogens to alkenes or to alkynes.* Dihalides or tetrahalides are formed (Chap. 5). Fluorine is so reactive, however, that tetrafluoromethane is formed.
2. *Addition of hydrogen halides to unsaturated halides or to alkynes* (Chap. 6).
3. *Reaction of hydrobromic or hydriodic acid with halogenated alcohols.*



Dehydrohalogenation of polyhalogenoalkanes to halogenated alkenes.



Some polyhalogen compounds are listed in Table 34. When two or more halogen atoms are attached to the same carbon atom, replacement reactions are much slower, but ease of dehydrogenation usually is increased.

TABLE 34 | **Constants of Some Polyhalogen Compounds**

NAME	CHLORIDE		BROMIDE			IODIDE	
	b.p. °C	sp gr.	b.p. °C	sp. gr.	m.p. °C	b.p. °C	sp. gr.
Dihalomethane	39.8	1.336	98.6	2.49	5.7	180 [c]	3.325
Trihalomethane	61.2	1.489	151.2	2.89	119	subl	4.008
Tetrahalomethane	76.7	1.595	189.5	3.42	[c]	subl.	4.32
1,1-Dihaloethane	57.3	1.174	110	2.056		179	2.84
1,2-Dihaloethane	83.7	1.257	131.7	2.180	82	[c]	2.13
1,2-Dihaloethylene (*cis*)	60.3	1.291	110	2.28	−13.8	188 [c]	3.06
1,2-Dihaloethylene (*trans*)	48.4	1.265	108	2.26	73	192	3.30
1,1-Dihalopropane	87.0	1.143 [a]	130				
1,2-Dihalopropane	96.8	1.159	142	1.933		[c]	2.490
1,3-Dihalopropane	120.4	1.201 [b]	167	1.979	−13	224 [c]	2.51
2,2-Dihalopropane	69.7	1.093	115	1.783		148 [c]	2.15
1,2,3-Trihalopropane	158	1.391	220	2.436	16		

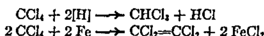
[a] At 10°. [b] At 15°. [c] Decomposes.

Methylene iodide, CH_2I_2, has about the highest density of any liquid except mercury and is used by mineralogists in determining the density of minerals and in separating them from each other. For this purpose it is usually mixed with liquids of lower density. It is prepared by the reduction of iodoform, CHI_3, by it heating with hydriodic acid and phosphorus or, more conveniently, with sodium arsenite solution.



$$CHI_3 + Na_3AsO_3 + NaOH \longrightarrow CH_2I_2 + NaI + Na_3AsO_4$$

Chloroform, $CHCl_3$, trichloromethane, is produced industrially by the direct chlorination of methane and also from carbon tetrachloride by slow reduction with iron and water. Tetrachloroethylene is a by-product.

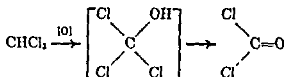


$$CCl_4 + 2[H] \longrightarrow CHCl_3 + HCl$$
$$2\,CCl_4 + 2\,Fe \longrightarrow CCl_2{=}CCl_2 + 2\,FeCl_2$$

This process is more economical than the older one, in which ethyl alcohol or acetone is heated with a suspension of bleaching-powder or with a solution of sodium hypochlorite. The reactions involved, which are somewhat complicated, are described in Chapter 17 under the Haloform Reaction.

Chloroform is a sweet-smelling liquid, nonflammable, and only slightly soluble in water. It was formerly used extensively in anesthesia but has been largely displaced by ether and ethylene, which do not affect the heart adversely as chloroform does. It is an excellent solvent for many organic substances such as fats, oils, etc.

Chloroform when heated with an oxidizing agent, such as sulfuric acid and a dichromate, is oxidized to the poisonous gas phosgene, $COCl_2$.



The intermediate compound written in brackets is unstable and has never been isolated, for it easily loses hydrogen chloride to form phosgene. When chloroform is exposed to light and air, phosgene is formed. The addition of a small amount of alcohol prevents to a large extent the formation of phosgene. Chloroform should be stored in the dark and kept in dark-colored bottles. When heated with potassium hydroxide in alcohol, it forms potassium formate.



$$HCCl_3 + 4\,KOH \longrightarrow HCOOK + 3\,KCl + 2\,H_2O$$

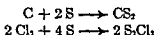
Iodoform, CHI_3, triiodomethane, is prepared by the action of iodine and aqueous alkali upon alcohol, acetone, or a few other compounds (see Chaps. 10, 17). The reactions are analogous to those used for the preparation of chloroform. It is also prepared by the electrolytic oxidation at 60° of an aqueous solution of alcohol containing carbonate and iodide ions. Iodoform is used as an antiseptic but because of its unpleasant odor has been largely displaced by other substances.

Carbon tetrachloride, CCl_4, is the final product of the action of chlorine on methane (see p. 118). The process which has been used for many years allows it to be made essentially from carbon and chlorine, through the intermediate of sulfur compounds. Carbon disulfide gives carbon tetrachloride with chlorine (catalyzed by iodine) or with sulfur monochloride (catalyzed by iron or iron chloride).



$$3\,Cl_2 + CS_2 \longrightarrow CCl_4 + S_2Cl_2$$
$$S_2Cl_2 + CS_2 \longrightarrow CCl_4 + 6\,S$$

Carbon disulfide and sulfur monochloride are regenerated from sulfur with carbon and chlorine, respectively.



$$C + 2\,S \longrightarrow CS_2$$
$$2\,Cl_2 + 4\,S \longrightarrow 2\,S_2Cl_2$$

Carbon tetrachloride is an important industrial compound, for it is one of the few nonflammable organic solvents. It readily dissolves fats, oils, and other nonpolar liquids and is used for extracting such substances. Because of its volatility it is used for the dry cleaning of clothes. Generally a mixture of gasoline and carbon tetrachloride constitutes the usual cleaning solvent, the amount of the latter being sufficient to render the mixture incombustible. Carbon tetrachloride is used for extinguishing fires. However, some danger is associated with its use for this purpose, since it may be converted, by reaction with steam, to phosgene.



$$CCl_4 + H_2O \longrightarrow COCl_2 + 2\,HCl$$

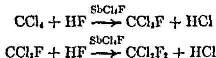
Nevertheless, it is of some value in controlling fires of burning liquids which are nonmiscible with water, such as oils. When water is added in such cases, the fire is spread, but when carbon tetrachloride is added, the latter evaporates and the heavy cloud of vapor smothers the fire.

Fluorinated Methanes. Carbon tetrachloride reacts with hydrogen fluoride in the presence of $SbCl_4F$, which is obtained by a reaction between antimony pentachloride and hydrogen fluoride.



$$SbCl_5 + HF \longrightarrow SbCl_4F + HCl$$

The replacement of a chlorine by a fluorine atom is catalyzed by this antimony fluorochloride.

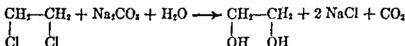


$$CCl_4 + HF \xrightarrow{SbCl_4F} CCl_3F + HCl$$

$$CCl_3F + HF \xrightarrow{SbCl_4F} CCl_2F_2 + HCl$$

The two products, trichlorofluoromethane, b.p., 23.8°, and dichlorodifluoromethane, b.p. −30°, f.p. $< -160°$, are nonflammable, nonirritating, relatively nonpoisonous gases extensively used as refrigerants. They are called Freon-11 and Freon-12, respectively.

Ethylene chloride, CH_2ClCH_2Cl, is prepared by the reaction of chlorine with ethylene under controlled conditions below 200°. It is employed industrially as a solvent, and for the manufacture of ethylene glycol, by heating with aqueous sodium carbonate under pressure at temperatures of 150 to 175°.



$$\underset{Cl}{CH_2}-\underset{Cl}{CH_2} + Na_2CO_3 + H_2O \longrightarrow \underset{OH}{CH_2}-\underset{OH}{CH_2} + 2\,NaCl + CO_2$$

Also, it is converted to vinyl chloride when heated with caustic alkalies.



$$CH_2Cl-CH_2Cl + NaOH \longrightarrow CH_2{=}CHCl + NaCl + H_2O$$

Ethylene bromide, CH_2BrCH_2Br, is prepared from bromine and ethylene. It is added to gasoline containing tetraethyllead in order to convert metallic lead, a decomposition product of the antiknock, to lead bromide, which has a less harmful action on the internal-combustion engine.

Ethylene iodide, CH_2ICH_2I, may be prepared by passing ethylene into an alcoholic solution of iodine, the less soluble iodide separating out. The iodide, on standing in the open, slowly disappears owing to its dissociation into ethylene and iodine. The reaction, therefore is reversible,



$$C_2H_4I_2 \rightleftharpoons C_2H_4 + I_2$$

and the equilibrium constant for the vaporized iodide,

$$K = \frac{[C_2H_4][I_2]}{[C_2H_4I_2]}$$

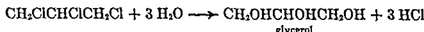
has a value of 6.3 at 15°, 28.3 at 30°, and 129 at 50°. It is characteristic of 1,2-diiodo compounds (iodine on adjacent carbon atoms) that they readily decompose into iodine and an unsaturated compound.

Acetylene dichloride, $CHCl{=}CHCl$, 1,2-dichloroethylene, and **acetylene tetrachloride, $CHCl_2CHCl_2$,** 1,1,2,2-tetrachloroethane, b.p. 146°. These can be prepared by the addition of chlorine to acetylene. The first is a mixture of the *cis* and *trans* isomers, b.p. 60° and 48°, respectively. Both are good solvents for oils. The tetrachloride is not combustible but is quite toxic; it undergoes hydrolysis and reacts with metals under some conditions. By heating the tetrachloride with a base, such as lime or ammonia, it is converted quantitatively to trichloroethylene.

Trichloroethylene, $CCl_2{=}CHCl$, b.p. 87°, is noncombustible and is used extensively as a solvent for fats, waxes, resins, rubber, and many other substances.

1,2,3-Trichloropropane, $CH_2ClCHClCH_2Cl$, is prepared by the controlled addition of chlorine to allyl chloride (p. 117). This is an important step in a synthetic

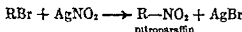
process of producing glycerol. Trichloropropane is converted to glycerol by heating with water.



$$CH_2ClCHClCH_2Cl + 3\ H_2O \longrightarrow \underset{\text{glycerol}}{CH_2OHCHOHCH_2OH} + 3\ HCl$$

Differentiation of Halogen Compounds. Silver nitrate in alcohol reacts at different rates with halogen compounds. Saturated alkyl halides react in the order: iodide > bromide > chloride and tertiary > secondary > primary. Unsaturated allyl type compounds are quite reactive and vinyl type are unreactive. At room temperature alkyl iodides, allyl chlorides, bromides, and iodides, tertiary bromides, and tertiary chlorides usually produce a precipitate or cloudiness within less than a minute. Primary chlorides become cloudy in $\frac{1}{2}$ to 1 hour. Polyhalides like chloroform and carbon tetrachloride are unreactive.

Primary, secondary, and tertiary alkyl halides may be differentiated by conversion, by means of silver nitrite, to primary, secondary, and tertiary nitroparaffins respectively, and these can be differentiated easily by the so-called red, white, and blue reaction (Chap. 24).



$$RBr + AgNO_2 \longrightarrow \underset{\text{nitroparaffin}}{R{-}NO_2} + AgBr$$

With nitrous acid primary nitroparaffins give a product which is red in basic solution, secondary give a blue colored compound, and tertiary nitroparaffins are not affected.

PROBLEMS

1. Write balanced equations for the reactions involved in three methods of preparing the following with three different reagents

a) 1-bromopropane from 1-hydroxypropane
b) 1-bromobutane from 1-hydroxybutane
c) 1-chloropropane from 1-hydroxypropane
d) 1-chlorobutane from 1-hydroxybutane
e) 2-iodopropane from 2-hydroxypropane

2. Write balanced equations for reactions involved in a practical laboratory preparation of the following, starting with *n*-butyl bromide.

a) *n*-octane
b) 1-hexyne
c) 1-hexene
d) *n*-hexane
e) *n*-butane
f) 1-butene
g) 1-hydroxybutane
h) 1,2-dibromobutane
i) *n*-butylmercaptan
j) *n*-butylamine
k) *n*-butyl cyanide
l) *n*-butyl sulfide
m) *n*-butyl sulfate
n) *n*-butyl nitrite
o) *n*-butyl acetate
p) 5-decyne
q) *n*-butylmagnesium bromide
r) 5-decene

3. Write balanced equations for the reactions involved in a practical laboratory preparation of the following, starting with isoamyl iodide.

a) 2,7-dimethyloctane
b) isoamylzinc bromide
c) isoamylmagnesium bromide
d) 3-methyl-1-butene
e) 3-iodo-2-methylbutane
f) 2-methylbutane
g) 5-methyl-1-hexyne
h) 5-methyl-1-hexene
i) 1,2-dibromo-5-methyl-1-hexene
j) 4-hydroxy-2-methylbutane
k) isoamyl cyanide
l) isoamyl sulfide
m) 5,6-dibromo-2-methylhexane
n) isoamyl nitrite
o) isoamyl isocyanide
p) isoamyllithium
q) isoamyl sulfate
r) isoamylamine
s) sodium 3-methylbutane-1-sulfonate
t) 4-nitro-2-methylbutane

4. Indicate the steps (using arrow, reagent, and conditions) by which 2-bromo-2-butene may be obtained from

a) methylacetylene
b) acetylene
c) 2,3-dibromobutane
d) 2-butene

5. Write electronic formulas of the following and indicate if resonance is possible or not.

a) ethyl fluoride
b) *sec*-butyl iodide
c) 2-chloropropene
d) 1,3-dibromopropane
e) 1,1-dichloro-4-bromobutane
f) 3-bromo-1-butene
g) 1,2-dichloro-2,3-difluoropropane
h) 1-chloro-2-methylpropene
i) 4-fluoro-2-methyl-2-butene
j) 2-chloro-1-butyne
k) 3-chloro-1-butyne
l) 4-chloro-1-butyne

6. Describe a reasonably rapid chemical test, stating reagent, conditions, solvent if any, and readily detectable change, that serves to distinguish between:

a) carbon tetrachloride and *n*-butyl chloride
b) 1-bromopropane and 1-bromopropene
c) 3-bromopropene and 3-bromopropyne
d) *n*-butyl chloride and *tert*-butyl chloride
e) *n*-butyl chloride and *n*-butyl iodide
f) 1-bromopropane and 3-bromopropene
g) 1,2-dibromobutane and 1,4-dibromobutane
h) 2-bromobutane and 2-bromo-1-butene
i) 1,2-dichlorethane and 1,2-dichloroethylene
j) tetrachloroethylene and 1,1,2,2-tetrachloroethane
k) allyl bromide and *n*-propyl bromide
l) crotyl chloride and *n*-butyl chloride
m) 1-bromopentane and 2-bromo-2-methylbutane
n) 1-bromobutane and 1-bromo-1-butene
o) 1-bromobutane and 2-bromo-1-butene
p) 1-bromobutane and 3-bromo-1-butene

7. Name the following:

a) $CH_3C(CH_3)_2CBr_2CH_3$
b) $ClCH_2CBr_2CH_2CH_3$
c) $(CH_3)_2CHCBr_2CBr_2CH_3$
d) $BrCH_2CH{=}CHCH_2Br$
e) $BrCH_2C(CH_3)_2CH{=}CH_2$
f) $F_3CCH_2CH{=}C(CH_3)_2$
g) $ClCH{=}CClCCl(CH_3)_2$
h) $(CH_3)_2C(CH_2CH_2Cl)CH_2CH_2Br$
i) $CH_2{=}CBrCH(CH_3)CH{=}CH_2$
j) $FH_2CCH_2CBr{=}CBrCH(CH_3)_2$
k) $(CH_3)_2(CH_2)_2CH(CHClCH_2Cl)_2$
l) $HC{\equiv}CCH(CH_2Br)CH_2CH{=}CH_2$

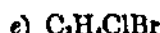
8. Write the structures and names of the theoretically possible isomeric (including geometrically isomeric but excluding cyclic) compounds of the formula:


a) $C_3H_6Br_2$


b) $C_3H_5Br_3$

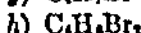

c) $C_3H_4Cl_2$


d) C_3H_6ClBr

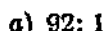

e) C_3H_4ClBr

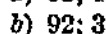

f) $C_4H_8Cl_2$


g) C_4H_7Br

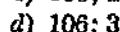

h) $C_4H_8Br_2$

9. Write the structure of an alkyl chloride having a molecular weight indicated by the first number, and structurally isomeric monochloro derivatives indicated by the second number (those having one more chlorine atom).

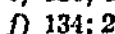

a) 92; 1


b) 92; 3

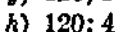

c) 106; 2


d) 106; 3


e) 120; 4


f) 134; 2


g) 120; 3


h) 120; 4

10. An organic bromine compound, *A*, reacted with metallic sodium. There was obtained compound *B* which had no bromine. It boiled at 180–184°. What was *A*?

11. Compound *A* boils at 70–71°. When a drop is added to alcoholic silver nitrate a precipitate is formed rapidly. The compound causes rapid decolorization of bromine in carbon tetrachloride, and rapid formation of a dark precipitate with aqueous potassium permanganate. What is *A*?

CHAPTER 9

Organometallic Compounds

Organometallic compounds are those in which the metal atom is in combination with carbon. Salts of typical organic acids, *e.g.*, RCOONa and RSO_2ONa, are not included, for in these the metal is in combination with oxygen. Typical examples of organometallic compounds are shown below.

CH_3Na	C_2H_5MgI	$(C_2H_5)_2Zn$	$(CH_3)_2Hg$	$(C_2H_5)_4Pb$
methylsodium	ethylmagnesium iodide	diethylzinc	dimethylmercury	tetraethyllead

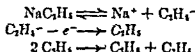
Organometallic compounds differ markedly in properties. At the one extreme are solids like methylsodium which is an ionic compound of high reactivity, and at the other are liquids like dimethylmercury and tetraethyllead, which resemble covalent compounds in possessing slight chemical reactivity. Although the alkylsodiums are little used, due to inconvenience of preparation, their interesting properties warrant some discussion.

Ethylsodium, Sodium Ethide, NaC_2H_5. This is prepared by the action of metallic sodium upon diethylzinc or diethylmercury.



$$(C_2H_5)_2Zn + 2\ Na \longrightarrow 2\ C_2H_5Na + Zn$$

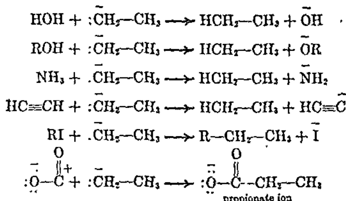
It is a solid which, when dissolved in diethylzinc (or triethylaluminum), is an electrolyte and conducts the electric current, zinc appearing at the cathode and a hydrocarbon mixture, largely ethane and ethylene, appearing at the anode.



$$NaC_2H_5 \rightleftharpoons Na^+ + C_2H_5^-$$
$$C_2H_5^- - e^- \longrightarrow C_2H_5$$
$$2\ C_2H_5 \longrightarrow C_2H_6 + C_2H_4$$

It is believed that ethylsodium ionizes into positive sodium and negative ethide ions and that free ethyl, liberated at the anode by loss of an electron, reacts to form ethane and ethylene.

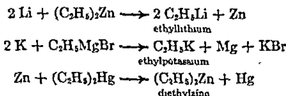
Sodium ethide is an extremely reactive substance. It inflames in the air and is decomposed rapidly by any substance furnishing active hydrogen, as for example water, an acid, an alcohol, ammonia, or even acetylene. Also it reacts rapidly with an alkyl halide and with carbon dioxide.



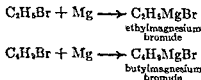
The formation of ethane in the first four reactions above shows that the reacting substances are acidic relative to ethane, which is liberated from its salt, sodium ethide, by the action of a stronger acid. These are themselves very weak acids by the usual standards, but strong relative to ethane, which has a constant of the order of about 10^{-40}.

The high reactivity of sodium ethide is due to the negative ethide ion in the same way that the high reactivity of sodium acetylide is due to the negative acetylide ion (p. 85). Sodium ethide is a more strongly nucleophilic reagent than sodium acetylide, since ethane is a very much weaker acid than acetylene. Reaction takes place easily with many compounds in which a carbon atom forms the positive end of a dipole, as in carbon dioxide (p. 86), in organic carbonyl (C=O) compounds, and in alkyl halides (Table 15, p. 33). The equations above are written to show that the reactions involve a negatively charged carbon atom in ethide ion, and that this becomes attached to the less electronegative atom of the reactant.

Other organometallic compounds may be prepared by the same type of reaction described above for methylsodium, *i.e.*, the displacement of the metal atom of an organic metallic compound by a more active metal.

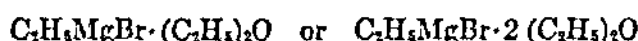


Grignard Reagents, RMgX. An alkylmagnesium halide is formed when magnesium reacts with an alkyl halide in absolute (water- and alcohol-free) ether.



Grignard in 1900 prepared many compounds of this type and studied their reactions. *His name is associated with these compounds because of his ex-*

tensive investigations, although the discovery of this type of compound was made by Barbier. Grignard reagents have proved to be extremely valuable *in synthesis because they are easily prepared and undergo a wide variety of* easily carried out reactions. Evaporation of the ether in the absence of moisture, oxygen, and carbon dioxide leaves a solid "etherate," or coordination compound involving one or two molecules of solvent:

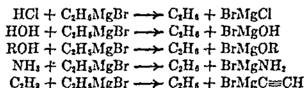


$$C_2H_5MgBr \cdot (C_2H_5)_2O \quad \text{or} \quad C_2H_5MgBr \cdot 2\,(C_2H_5)_2O$$

It is not necessary to isolate the Grignard reagents, for they react rapidly in the ether solution.

Grignard reagents react with:

1. *Compounds having active hydrogen*, such as acids, water, alcohols, ammonia, acetylene, etc., to form the alkane. These reactants are stronger acids than the alkane and thus are able to decompose a salt of a weaker acid. The other products are MgBr salts of these acids, or essentially mixtures of magnesium bromide and the magnesium salt of the other acids.

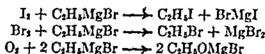


$$HCl + C_2H_5MgBr \longrightarrow C_2H_6 + BrMgCl$$
$$HOH + C_2H_5MgBr \longrightarrow C_2H_6 + BrMgOH$$
$$ROH + C_2H_5MgBr \longrightarrow C_2H_6 + BrMgOR$$
$$NH_3 + C_2H_5MgBr \longrightarrow C_2H_6 + BrMgNH_2$$
$$C_2H_2 + C_2H_5MgBr \longrightarrow C_2H_6 + BrMgC{\equiv}CH$$

These reactions are the second step in the replacement of a halogen atom of an alkyl halide by hydrogen (reduction of an alkyl halide) by means of metallic magnesium. The rapidity of the reaction with water emphasizes the necessity of excluding moisture.

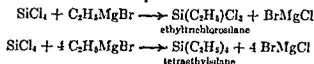
In the Zerevitinow method of determining active (labile) hydrogen the reagent is methylmagnesium iodide. The methane evolved is collected and the volume is measured.

2. *Halogens and oxygen.* These reactions show that Grignard reagents are reducing agents. Because they react readily with oxygen, Grignard reagents should not be exposed needlessly to air.



$$I_2 + C_2H_5MgBr \longrightarrow C_2H_5I + BrMgI$$
$$Br_2 + C_2H_5MgBr \longrightarrow C_2H_5Br + MgBr_2$$
$$O_2 + 2\,C_2H_5MgBr \longrightarrow 2\,C_2H_5OMgBr$$

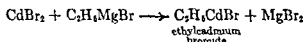
3. *Many inorganic halogen compounds.* Reaction takes place with a large number of inorganic halides. These are halides of nonmetals, of metalloids, and of those metals that form less reactive organometallic compounds, but not with halides of elements more strongly metallic than magnesium.

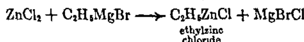


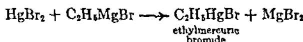
$$SiCl_4 + C_2H_5MgBr \longrightarrow \underset{\text{ethyltrichlorosilane}}{Si(C_2H_5)Cl_3} + BrMgCl$$
$$SiCl_4 + 4\,C_2H_5MgBr \longrightarrow \underset{\text{tetraethylsilane}}{Si(C_2H_5)_4} + 4\,BrMgCl$$

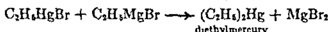
One, two, three, or four of the chlorine atoms of silicon tetrachloride may be replaced by alkyl radicals. Other nonmetallic halides that also react step-

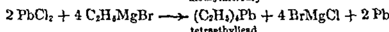
wise are phosphorus trichloride and arsenic trichloride. Metallic halides that react are numerous.











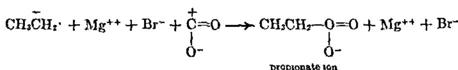
4. *Some organic halides.* Tertiary alkyl halides and allyl halides react. The reaction with the latter is a valuable method for the preparation of 1-alkenes (Chap. 5). Acyl halides also react. Coupling similar to the Wurtz coupling is brought about by some heavy metal halides, for example, cuprous chloride.

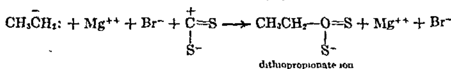


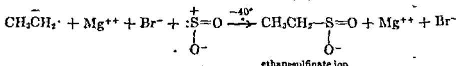




5. *Carbon dioxide and many other compounds* possessing a carbonyl (C═O) double bond, or other multiple bond of significant dipole moment (Table 15, p. 33) such as C═S, S═O, and C≡N. The reactions with such compounds are similar to those of carbon dioxide with sodium propynide (p. 86) and with sodium ethide (ethylsodium). For this type of reaction it is convenient to write the Grignard reagent in the form of ions, so as to emphasize its similarity to sodium acetylide and sodium ethide, and to write the other reactant in the dipolar reactive form.

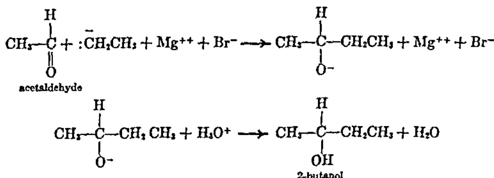






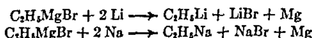
On the addition of a strong acid to the reaction mixtures the products obtained are, respectively, propionic acid, dithiopropionic acid, and ethanesulfinic acid.

6 *Many types of organic compounds.* The most important reactions of Grignard reagents are those with organic carbonyl (C=O) compounds, *viz.*, aldehydes, R—CHO, ketones, $R_2C=O$, and esters, R—CO—OR, for preparation of alcohols (Chap. 10), and with organic cyanides, R—C≡N, for the preparation of ketones (Chap. 17). The reaction with acetaldehyde is typical.



The product obtained with acetaldehyde is a secondary alcohol, 2-butanol. Ketones yield tertiary alcohols (Chaps. 10, 16). Grignard reagents react also with ethylene oxide (Chap. 11) and with acyl halides RCOCl (Chap. 15).

7. *Metals, mainly the alkali metals,* to form more reactive organometallic compounds. The more metallic elements displace magnesium.



Reactivity of Grignard Reagents. It is seen that Grignard reagents and alkylsodiums undergo similar reactions, except that the sodium compounds are much more reactive, and also undergo other reactions, such as the Wurtz coupling and addition to alkenes. This is because sodium is a more active metal, forcing its electron upon the carbon atom, thus producing a highly reactive alkide ion (see p. 126). A Grignard reagent dissociates into a positive alkylmagnesium and negative bromide ion.



A second ionization into positive magnesium and negative ethide ions



would make the analogy with ethylsodium complete. Only a small concentration of ethide ion would suffice to account for the reactivity, because more would be formed by dissociation. Evidence indicating a second dissociation, as written, is not conclusive. Even if ethide ion is not present as such, the carbon-to-magnesium bond has such a large amount of ionic character that when the bond is broken the electron pair of the bond remains with the carbon atom. The Grignard reagent is thus a strongly nucleophilic reagent but not such an outstanding one as sodium ethide.

Organolithium Compounds. These are prepared like Grignard reagents, but usually with a hydrocarbon solvent, for example, benzene, C_6H_6, to minimize the Wurtz coupling, which is faster in ether solution.



$$CH_3CH_2CH_2Cl + 2\,Li \longrightarrow \underset{n\text{-propyllithium}}{CH_3CH_2CH_2Li} + LiCl$$

Chlorides are preferred, because they couple only slowly with the resulting organometallic compound. Alkyl iodides are so reactive that in ether solution essentially no alkyllithium can be prepared, owing to the speed of the coupling reaction.



$$C_2H_5Li + C_2H_5I \longrightarrow C_2H_5{-}C_2H_5 + LiI$$

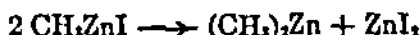
Thus the lithium compounds in general are intermediate in reactivity between the sodium compounds and Grignard reagents. They are being used more in synthetic work, because of ease of preparation and excellent reactivity.

Organozinc Compounds. The zinc compounds are the longest-known organometallic compounds. They were discovered in 1849 by Frankland. Methylzinc iodide is formed when methyl iodide is heated with zinc filings.



$$CH_3I + Zn \longrightarrow CH_3ZnI$$

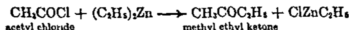
This decomposes when heated strongly and dimethylzinc distils.



$$2\,CH_3ZnI \longrightarrow (CH_3)_2Zn + ZnI_2$$

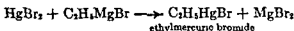
Dimethylzinc is a repugnent smelling liquid inflaming on exposure to air. It is important historically because the combining power of zinc was shown by vapor density determination to be two. It is a nonconductor and is one of the few liquids that will dissolve ethylsodium and other similar compounds without causing decomposition. The solution of ethylsodium is electrically conducting, indicating that ethylsodium dissociates into negative ethyl and positive sodium ions.

Dialkylzincs are decomposed by water, alcohols, acids, and ammonia. They react only slowly with carbon dioxide. Often these compounds are handled in an atmosphere of carbon dioxide, to prevent ignition. Formerly they were much used in synthesis but have been largely supplanted by Grignard reagents. They react only slowly with aldehydes and ketones, yielding alcohols. They react with acid chlorides to yield ketones.

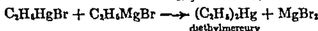


$$\underset{\text{acetyl chloride}}{CH_3COCl} + (C_2H_5)_2Zn \longrightarrow \underset{\text{methyl ethyl ketone}}{CH_3COC_2H_5} + ClZnC_2H_5$$

Organomercury Compounds. There are two types, as, for example, ethylmercuric halide and diethylmercury. They are obtained by the action of a mercuric halide with a Grignard reagent.

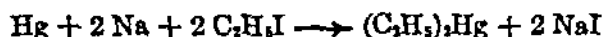


$$HgBr_2 + C_2H_5MgBr \longrightarrow \underset{\text{ethylmercuric bromide}}{C_2H_5HgBr} + MgBr_2$$



$$C_2H_5HgBr + C_2H_5MgBr \longrightarrow \underset{\text{diethylmercury}}{(C_2H_5)_2Hg} + MgBr_2$$

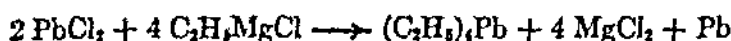
The last may be obtained directly from mercury, metallic sodium, and ethyl iodide.



$$Hg + 2\,Na + 2\,C_2H_5I \longrightarrow (C_2H_5)_2Hg + 2\,NaI$$

Alkylmercuric halides are solids of convenient melting points. They are useful in the identification of alkyl halides. The mercury alkides, R_2Hg, are volatile, highly poisonous liquids, much less reactive than the corresponding zinc compounds. They are not changed when exposed to oxygen or moisture at the ordinary temperature but will inflame when heated in the air.

Organolead Compounds. **Tetraethyllead, $(C_2H_5)_4Pb$,** is the best known of the lead alkides, for it is used extensively in gasoline as an antiknock. It may be prepared by the reaction of ethyl magnesium chloride with lead chloride.



$$2\,PbCl_2 + 4\,C_2H_5MgCl \longrightarrow (C_2H_5)_4Pb + 4\,MgCl_2 + Pb$$

The methyl and *n*-propyl compounds may be obtained similarly. Tetraethyllead is manufactured from ethyl chloride and one of the lead-sodium alloys, NaPb.



$$4\,NaPb + 4\,C_2H_5Cl \longrightarrow (C_2H_5)_4Pb + 4\,NaCl + 3\,Pb$$

It is a highly poisonous liquid, boils at 202°, is soluble in organic liquids like gasoline, insoluble in and not decomposed by water.

The pyrolysis of organolead compounds has shown that free alkyl radicals can exist, but only for a very short time, and at low partial pressures. When the vapor of tetramethyllead, $(CH_3)_4Pb$, is mixed with nitrogen and passed through a hot tube, the lead compound is decomposed, the principal products being lead and ethane. When a thin film of metallic lead is placed in the reaction gas after it has passed through the heated zone, the lead slowly disappears, but if the film is moved some distance away from the heated zone, no lead is removed. The removal of the lead is believed to be due to the formation of volatile tetramethyllead by a reaction with free methyl radicals,



$$Pb + 4\,CH_3 \longrightarrow (CH_3)_4Pb$$

and the free methyl radicals are believed to arise from the decomposition of tetramethyllead at the higher temperature.



$$(CH_3)_4Pb \longrightarrow Pb + 4\,CH_3$$

From the rate of gas flow, the rate of removal of lead from the lead film, and the distance of the film from the heated zone, the half-life of the methyl radical, that is, the time necessary for one half to disappear, has been calculated to be 0.006 second, under the conditions of the experiment. The radicals disappear rapidly, by combining to form ethane.

Reactivity and Ionic Character. In general, the organometallic compounds of the strongest metals are the most reactive and have physical properties similar to those of ionic compounds (Chap. 3), as in the case of ethylsodium (Table 35). These characteristics are less pronounced in organometallic compounds of less metallic elements. Compounds of weak metals like mercury have properties of covalent, rather than of ionic substances. This is due to the fact that a strong metal like sodium donates an electron to the carbon atom, thus producing an ionic compound, whereas a weak metal like mercury forms a covalent bond with carbon by the sharing of electrons. It is seen from Table 35 that the nature of the metal determines the properties of the organometallic compound. The physical properties of diethylmercury are those expected of a compound of low dipole moment (Table 13, p. 31).

TABLE 35 | Properties of Some Organometallic Compounds

NAME	FORMULA	FORM	B.P. °C	CONDUCTIVITY	REACTIVITY
Ethylsodium	C_2H_5Na	solid	dec.	high in $(C_2H_5)_2Zn$	exceedingly high
Diethylmagnesium	$(C_2H_5)_2Mg$	solid	dec.		very high
Diethylzinc	$(C_2H_5)_2Zn$	liquid	118	low	medium
Diethylmercury	$(C_2H_5)_2Hg$	liquid	159	0	low

Similarity between Reactions of Sodium Alkynides and Organometallic Compounds. There is a close parallel between the products obtainable from reactive organometallic compounds, for example, the lithium compounds or Grignard reagents, and those from sodium alkynides. This is brought out in Table 36, where R, R′ and R″ may indicate the same or different alkyl radicals.

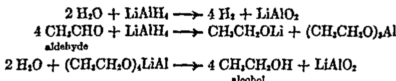
TABLE 36 | Resemblance between Grignard Reagents and Sodium Alkynides

REAGENT		PRODUCT		
		type of compound	from R′MgX	from R′C≡CNa
Water	H—O—H	hydrocarbon	R′H	R′C≡CH
Carbon dioxide	O=C=O	acid	R′—CO—OH	R′C≡C—CO—OH
Formaldehyde	H_2C=O	primary alcohol	R′—CH_2OH	R′C≡C—CH_2OH
Ethylene oxide	CH_2—CH_2 (bridged by —O—)	primary alcohol	R′—CH_2—CH_2OH	R′C≡C—CH_2—CH_2OH
Other aldehyde	R—C(=O)—H	secondary alcohol	R′—CHOH (—R)	R′C≡C—CH(—R)—OH
Ketone	R—C(=O)—R″	tertiary alcohol	R′—C(R)(R″)—OH	R′C≡C—C(R)(R″)—OH
Acid chloride	R—C(=O)—Cl	ketone	R′—C(=O)—R [a]	R′C≡C—C(=O)—R
Alkyl halide	R—X	hydrocarbon	R′—R [b]	R′C≡C—R

[a] Obtainable with alkylcadmium chloride, RCdCl, or alkylzinc chloride, RZnCl; alkylmagnesium halide reacts further, to give a tertiary alcohol.

[b] With certain halides, for example, tertiary halides or some higher halides, or with cuprous chloride.

Complex Metallic Hydrides. The most interesting of these newer type compounds is lithium aluminum hydride, $LiAlH_4$. It is mentioned here because it undergoes reactions that resemble those of reactive organometallic compounds, for example, lithium alkides and Grignard reagents. Thus it is decomposed by compounds having labile hydrogen (p. 127), and reduces carbonyl compounds (aldehydes, ketones, esters, anhydrides, and acyl halides) to alcohols.



$$2\,H_2O + LiAlH_4 \longrightarrow 4\,H_2 + LiAlO_2$$

$$\underset{\text{aldehyde}}{4\,CH_3CHO} + LiAlH_4 \longrightarrow CH_3CH_2OLi + (CH_3CH_2O)_3Al$$

$$2\,H_2O + (CH_3CH_2O)_4LiAl \longrightarrow \underset{\text{alcohol}}{4\,CH_3CH_2OH} + LiAlO_2$$

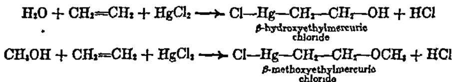
The product from an aldehyde actually is a salt of the alcohol and this yields the alcohol on the addition of water or of an aqueous acid. The reduction of a carbonyl compound is essentially an addition and is thus seen to be analogous to the reaction of a Grignard reagent, hydrogen instead of an organic radical becoming attached to the carbon atom. Lithium aluminum hydride is such a strong reducing agent it actually reduces a carboxylic acid to a primary alcohol.



$$4\,CH_3COOH + 3\,LiAlH_4 \longrightarrow CH_3CH_2OLi + (CH_3CH_2O)_3Al + 2\,LiAlO_2 + 4\,H_2$$

Lithium boron hydride, $LiBH_4$, is another excellent reducing agent, but weaker than the aluminum compound. It is not decomposed by water. For some purposes it is superior to lithium aluminum hydride because it can be used in contact with water. These reagents are proving to be of great value in structural determinations and in the synthesis of expensive organic chemicals.

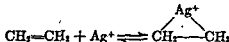
Organometallic Compounds from Olefins. Many unsaturated compounds react with salts of some of the heavier metals, with the formation of more or less unstable addition compounds. The mercuric compounds are the best known. Ethylene or other olefin slowly reacts with a mercuric halide in aqueous or alcoholic solution. The product is a reasonably stable solid.



$$H_2O + CH_2{=}CH_2 + HgCl_2 \longrightarrow \underset{\beta\text{-hydroxyethylmercuric chloride}}{Cl{-}Hg{-}CH_2{-}CH_2{-}OH} + HCl$$

$$CH_3OH + CH_2{=}CH_2 + HgCl_2 \longrightarrow \underset{\beta\text{-methoxyethylmercuric chloride}}{Cl{-}Hg{-}CH_2{-}CH_2{-}OCH_3} + HCl$$

The reactions are reversible and ethylene is regenerated on the addition of hydrochloric acid. There is some uncertainty in regard to the structure of the addition compounds above. Silver and cuprous salts also react with olefins. The products, consisting of a mole each of the olefin and the salt, are so much less stable than the mercuric compounds that ordinarily they cannot be isolated as such. Sometimes solutions of silver or cuprous salts are used for absorbing unsaturates from gaseous mixtures, for these are recovered merely by raising the temperature, or by lowering the pressure on the system. In the case of aqueous silver nitrate the reaction involves silver ion.



$$CH_2{=}CH_2 + Ag^+ \rightleftharpoons CH_2{-}CH_2 \text{ (bridged by } Ag^+\text{)}$$

The product is a simple coordination complex of the olefin and silver ion; its stability is due in part to the existence of more than one resonance form.

PROBLEMS

1. Write balanced equations for reactions involved in a practical preparation of the following, starting with an alkyl halide:

a) *n*-butylmagnesium bromide
b) isoamylmagnesium iodide
c) *t*-butylmagnesium chloride
d) *n*-butyllithium
e) *n*-amyllithium
f) *n*-propylzinc bromide
g) *s*-butylzinc iodide
h) di-*s*-propylmercury
i) *n*-butylmercuric chloride
j) isoamylmercuric bromide
k) *n*-propylsodium
l) *n*-butylpotassium
m) *n*-amylmercuric chloride
n) di-isoamylmercury
o) isopropylpotassium
p) isobutylsodium

2. State the reagent or reagents you would select and write equations for the reactions that you believe would take place in the preparation of the following from methylmagnesium iodide:

a) CH_3K
b) $CH_3—CO—OH$
c) CH_4
d) $CH_2{=}CHCH_2CH_3$
e) $(CH_3)_3Al$
f) CH_3HgI
g) $CH_3—SO—OH$
h) CH_3I
i) $(CH_3)_2CHOH$
j) CH_3Br
k) $(CH_3)_2Zn$
l) $(CH_3)_2Ba$
m) C_2H_5OMgBr
n) $(CH_3)_3P$
o) $(CH_3)_2SiCl_2$
p) $(CH_3)AsCl_2$
q) $(CH_3)_4Ge$
r) $(CH_3)_3As$
s) $(CH_3)_2Hg$
t) $(CH_3)_3SiCl$

3. State the reagent or reagents you would select, and write equations for the reactions which you believe would take place in the preparation of the following from *n*-butylmagnesium bromide:

a) *n*-butyllithium
b) *n*-butanesulfinic acid
c) *n*-butylmercuric bromide
d) *n*-butylzinc bromide
e) *n*-butyl iodide
f) *n*-butyltrichlorosilane
g) *n*-butylmercuric chloride
h) 3,3-dimethylheptane
i) *n*-butyldichlorophosphine
j) di-*n*-butyldichlorosilane
k) di-*n*-butylchloroarsine
l) *n*-butylcadmium chloride
m) tetra-*n*-butyltin
n) 1-heptene
o) 2-hydroxyhexane
p) tetra-*n*-butylsilane
q) tri-*n*-butylarsine
r) *n*-valeric acid
s) di-*n*-butylmercury
t) tri-*n*-butylphosphine

4. The following is to be so prepared, having only alkyl halides (saturated) available, that purification will be easy. Give equations for two satisfactory methods each involving a different metal, and different halides of fewer carbon atoms and different alkyl groups. Point out which method is superior, and why.

a) *n*-hexane
b) isohexane
c) *n*-octane
d) 2-methylheptane
f) 3-ethylhexane
g) 4-methylheptane
h) 2,2-dimethylhexane
i) 2,3-dimethylhexane

5. Show the steps (reactants and intermediate products) which you would select for the purpose of preparing the above compounds (Problem 4), using allyl bromide as one of the starting materials.

6. Write balanced equations for a practical laboratory preparation of the following, reasonably free of isomers, from compounds of fewer carbon atoms:

a) 1-butene
b) 1-pentene
c) 1-hexene
d) 4-methyl-1-pentene
e) 4-methyl-1-hexene
f) 5-methyl-1-hexene

CHAPTER 10

Monohydric Alcohols, $C_nH_{2n+1}OH$

Alcohols are hydroxy derivatives of the hydrocarbons. The hydroxyl radical, OH, is the characteristic functional group of the alcohols. More than one hydroxyl radical may be present in a molecule. Although such a compound is classified as an alcohol, the word *alcohol*, as used in nomenclature, is limited to the monohydroxy compounds.

As monohydroxy substitution products of the hydrocarbons the alcohols are also oxidation products in the sense that they contain more oxygen than the hydrocarbons themselves. It is usually not possible to obtain alcohols directly from hydrocarbons since the oxidation goes too far. However, methanol, the monohydroxy derivative of methane, has been obtained as a by-product in the catalytic gas phase oxidation of methane to formaldehyde at high temperatures with an amount of air insufficient for complete oxidation. This would appear to indicate that methanol is the product of the first step in the oxidation of methane.

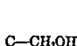
The alcohols may also be looked upon as derived from water, one of the hydrogen atoms of which is replaced by a univalent organic radical. Since the alcohols, especially the lower ones, resemble water in many of their characteristic properties, it will be profitable later on to describe them in the light of this relationship.

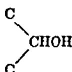
Nomenclature. Alcohols are named in three ways: (*a*) as alkyl alcohols; for example, methyl alcohol, ethyl alcohol, etc. These are the common names, most of which have been in use for decades. This method is useful for alcohols up to and including the butyl alcohols, but for higher alcohols too many prefixes are necessary. (*b*) As derivatives of the first member of the series, CH_3OH, which for this purpose is called **carbinol.** This method is satisfactory up to and including the pentyl (amyl) alcohols; but above, too many prefixes are necessary. (*c*) By the I.U.C. system. The longest chain containing the hydroxyl group is selected, the chain is numbered so as to give the hydroxyl group the lower number and substituents are indicated by name and position. The three methods are illustrated by the names of the butyl alcohols shown in Table 37. Sometimes the number follows the name, as butanol-1.

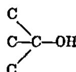
TABLE 37 | Nomenclature of Butyl Alcohols

FORMULA	COMMON NAME	CARBINOL NAME	I.U.C. NAME
$CH_3CH_2CH_2CH_2OH$	normal butyl alcohol	n-propylcarbinol	1-butanol
$CH_3CH_2CHOHCH_3$	secondary butyl alcohol	methylethylcarbinol	2-butanol
$(CH_3)_2CHCH_2OH$	isobutyl alcohol	isopropylcarbinol	2-methyl-1-propanol
$(CH_3)_3COH$	tertiary butyl alcohol	trimethylcarbinol	2-methyl-2-propanol

Alcohols are classified as primary, secondary, and tertiary on the basis of the number of carbon atoms attached to C—OH as follows.

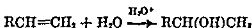

primary alcohol


secondary alcohol


tertiary alcohol

General Methods of Preparation. Of these, hydration of olefins is important industrially in the manufacture of secondary and tertiary alcohols, and hydrolysis of alkyl chlorides is important in the manufacture of primary and secondary alcohols. The Grignard synthesis is much employed in research for the synthesis of higher alcohols. Reduction of esters is important in the manufacture of higher primary alcohols. The lower alcohols, methyl, *ethyl, and n-butyl in particular, are produced on a large scale by special* methods described in connection with these alcohols.

1. *Hydration of alkenes* (see p. 70). This reaction and the reverse reaction of dehydration of alcohols are described in more detail later under Reactions of Alcohols.



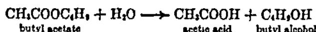
$$RCH{=}CH_2 + H_2O \xrightarrow{H_3O^+} RCH(OH)CH_3$$

2. *Hydrolysis of alkyl halides and of esters* (see p. 111). The hydrolysis of alkyl halides and the reverse reaction of alcohols with hydrogen halides are described in more detail later under Reactions of Alcohols.

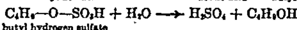


$$RCl + H_2O \longrightarrow ROH + HCl$$

Esters of organic and inorganic acids yield the alcohol and acid when hydrolyzed by heating with water.



$$\underset{\text{butyl acetate}}{CH_3COOC_4H_9} + H_2O \longrightarrow \underset{\text{acetic acid}}{CH_3COOH} + \underset{\text{butyl alcohol}}{C_4H_9OH}$$



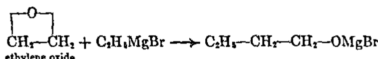
$$\underset{\text{butyl hydrogen sulfate}}{C_4H_9{-}O{-}SO_3H} + H_2O \longrightarrow H_2SO_4 + C_4H_9OH$$

Usually a base is added in the hydrolysis of an alkyl acetate; the reaction may be carried out in aqueous or alcoholic solution.

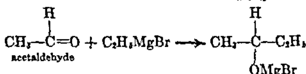


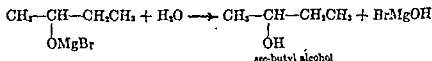
The bisulfate, usually a secondary or tertiary ester from the reaction of an alkene with sulfuric acid, hydrolyzes readily to the alcohol when heated with water.

3. *The Grignard synthesis.* Grignard reagents (Chap. 9) are much employed in the synthesis of higher alcohols. A primary alcohol is obtained with formaldehyde or ethylene oxide, a secondary with an aldehyde or ethyl formate, a tertiary alcohol with a ketone or ester other than a formate.

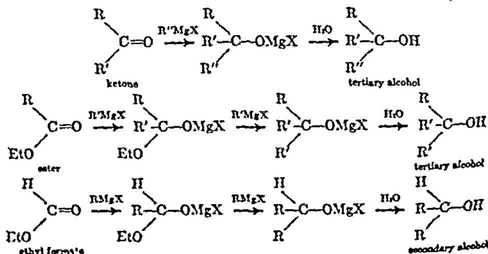








The first step is the formation of an addition compound, which is the bromomagnesium salt of the desired alcohol. The second step is the decomposition of this by the addition of water, for water is a stronger acid than an alcohol (Table 16, p. 35). The steps involved in other reactions are similar and are shown in outline form below. Esters differ in that they react with two moles of Grignard reagent. R, R′, and R″ represent univalent radicals; they may be alike or dissimilar.



4. *Reduction of aldehydes and ketones.* These can be reduced with sodium and alcohol, or with sodium amalgam and water. Hydrogenation methods also are available. The reactions are of interest in showing the relationship of alcohols to these compounds, for aldehydes are reduced to primary alcohols, ketones to secondary alcohols. The aluminum isopropoxide method is especially useful (Chap. 17).

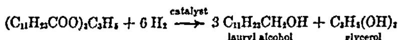


$$RCHO + 2\,Na + 2\,H_2O \longrightarrow RCH_2OH + 2\,NaOH$$



$$R_2CO + 2\,Na + 2\,H_2O \longrightarrow R_2CHOH + 2\,NaOH$$

5. *Reduction of derivatives of acids, viz.,* esters, acid chlorides, and acid anhydrides. The most important method here is the reduction of esters. Glycerides, the naturally occurring esters of fats, are reduced to primary alcohols (see Fats, Chap. 16).



$$(C_{11}H_{23}COO)_3C_3H_5 + 6\,H_2 \xrightarrow{\text{catalyst}} \underset{\text{lauryl alcohol}}{3\,C_{11}H_{23}CH_2OH} + \underset{\text{glycerol}}{C_3H_5(OH)_3}$$

6. *Reductions with lithium aluminum hydride* (p. 133). This will reduce aldehydes, ketones, esters, acid chlorides, acid anhydrides, and even acids to primary alcohols (Chaps. 9, 12). It is particularly useful in research but is too expensive for large scale operations.

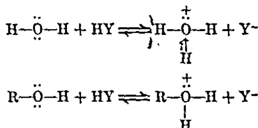
Properties of the Normal Monohydric Alcohols. Many of the physical properties are shown in Table 38. Water is included for purposes of comparison.

TABLE 38 | Normal Primary Alcohols

NAME	FORMULA	MELTING POINT °C	BOILING POINT °C	SPECIFIC GRAVITY 25°/4°	DIEL. CONST.	SOL. WATER G /100 G	HEATS COMB. KCAL./MOLE	K_a
(Water)	$H(OH)$	0.0	100.0	0.99765	81		0	1.8×10^{-16}
Methyl	$CH_3(OH)$	−97.0	64.5	.7890	31	misc.	173.64	1×10^{-17}
Ethyl	$C_2H_5(OH)$	−114.6	78.3	.78505	25	misc.	326.66 [a]	7.3×10^{-20}
Propyl	$C_3H_7(OH)$	−126.1	97.1	.7998	22	misc.	482.1	
Butyl	$C_4H_9(OH)$	−89.8	117.7	.8056	19	7.88	638.1	
Amyl	$C_5H_{11}(OH)$	−78.5	137.9	.8116	16	2.26	794.3	
Hexyl	$C_6H_{13}(OH)$	−51.6	156.5	.8158		0.63	950.6	
Heptyl	$C_7H_{15}(OH)$	−34.1	176.3	.8192		.18	1107.0	
Octyl	$C_8H_{17}(OH)$	−15.0	194.7	.8214		.05	1263.6	
Nonyl	$C_9H_{19}(OH)$	−5	213.5	.8230			1420.2	
Decyl	$C_{10}H_{21}(OH)$	6.0	228.0	.8300			1576.9	
Dodecyl	$C_{12}H_{25}(OH)$	24	143 [b]	.831				
Tetradecyl	$C_{14}H_{29}(OH)$	38	167 [b]	.824 [c]				
Cetyl	$C_{16}H_{33}(OH)$	49.3	190 [b]	.818 [c]				
Octadecyl	$C_{18}H_{37}(OH)$	58.5	210 [b]	.812 [c]				

[a] The heat of combustion of gaseous alcohol at 25° is 336.7 kg. cal.
[b] At 15 mm. [c] At melting point.

4. *Coordination compounds with acids; basic nature of alcohols.* Acids react rapidly with alcohols as they do with water, forming a positive **oxonium** ion and a negative acid ion.



Here HY represents an acid that undergoes ionization in the solvent. The proton parts company with the negative ion of the acid to become attached at an unshared electron pair of the oxygen atom of HOH or ROH. The extent of the reverse reaction is less, the stronger the acid. In water the reaction is essentially the ionization of the acid, and the extent of the reaction is a measure of the strength of the acid, as determined by conductivity measurements or other means. In an alcoholic solution the reaction is the ionization of the acid and at the same time a sort of neutralization of the acid by the alcohol, in the same sense as the neutralization of an acid by ammonia.

TABLE 39 | **Melting Points of Addition Compounds of Hydrogen Bromide with Alcohols**

HBr m.p. °C	ALCOHOL		ADDITION COMPOUND	
	formula	m.p. °C	formula	m.p. °C
−86	CH_3OH	−98	$CH_3OH \cdot HBr$	−12.8
	C_2H_5OH	−117	$C_2H_5OH \cdot HBr$	−28.5

The existence of an addition compound when liquid anhydrous hydrogen bromide is mixed with methyl alcohol or ethyl alcohol is shown by the data of Table 39. At a molal ratio of 1 to 1 the melting points of mixtures have maximum values, and these are the ones shown in the table. Thus the most stable addition compound is one composed of one mole of each of the reactants. The oxonium compounds are partly dissociated at their melting points and consequently are even more dissociated at room temperature. This is because the basicity of an alcohol, on which this reaction depends, is quite weak, for it is very much less than that of ammonia and comparable to that of water.

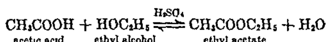
The basic nature of an alcohol therefore depends upon its ability to attract a proton, and not at all upon an ionization to give hydroxyl ions. In the presence of water the addition compounds are hydrolyzed to the alcohol and the hydrohalic acid.



$$CH_3\overset{+}{O}H_2 + Br^- + H_2O \rightleftharpoons CH_3OH + Br^- + H_3\overset{+}{O}$$

But in an aqueous solution having a sufficiently high concentration of hydronium ion as, for example, concentrated hydrochloric or hydrobromic acid, a higher alcohol, for example, *n*-butyl alcohol, is more soluble than in pure water, owing to the fact that the coordination compound is more soluble in water than is the alcohol. Alcohols as complex as octyl alcohol dissolve readily in concentrated sulfuric acid. This solubility is due largely to the oxonium reaction.

5. *Ester formation with acids.* Alcohols react with weak organic acids very slowly to form esters of organic acids, more rapidly in the presence of a strong acid, which acts catalytically. A typical reaction is the formation of ethyl acetate.

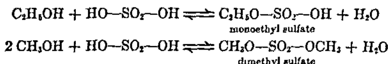


The relative rates of alcohols are in the order:

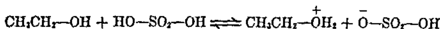


Only about two-thirds of the acid and alcohol react, because of reversibility. The reaction is described in more detail in Chapter 15 under Esterification.

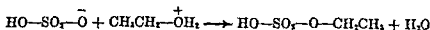
Strong acids usually react fairly rapidly when heated with the alcohol, especially sulfuric, hydrobromic, and hydriodic acids. In the liquid phase monoalkyl sulfates are formed with sulfuric acid. Dialkyl sulfates are obtained by rapid passage of the vapor of the reactants through hot reaction zones.



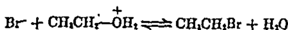
The reactions above do not tell the whole story, since an oxonium compound is first formed.



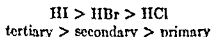
This is an important step in the formation of esters, for it is believed that the oxonium compound is more reactive than the alcohol. The increased ease of reaction can be ascribed to the greater ionic character of the carbon-to-oxygen bond or, in other words, to the greater bond dipole moment which is associated with the formal positive charge on the oxygen atom. The next step in the reaction is attack by the negative ion of the acid, leading to the formation of the ester and of water. This recalls the mechanism by which alkyl halides react with negative ions (p. 113).



Hydrohalic acids react to form alkyl halides (see Chap. 8). These may be regarded as esters of the alcohols with these acids.



The relative rates are in the orders:



$$HI > HBr > HCl$$
$$\text{tertiary} > \text{secondary} > \text{primary}$$

The difference in alcohols is shown by the action of concentrated hydrochloric acid on methyl and tertiary butyl alcohols. From the former, gaseous methyl chloride is slowly evolved after two or three days, and from the latter, liquid tertiary butyl chloride separates within a few seconds after mixing.

The reaction is the reversal of the hydrolysis of alkyl halides, one of the methods of preparing alcohols. The forward reaction is promoted by the use of anhydrous reagents or of concentrated aqueous hydrohalic acids. The reverse reaction is promoted by the presence of much water. Water influences the extent of the reaction not only through the operation of the mass action principle, but also much more importantly by the way it changes the free energy of formation of the substances involved in the reaction. The main effect is upon the hydrohalic acid. In the case of hydrogen bromide, ΔF of formation from the elements is -12.5 kcal. in the anhydrous state and -24.5 kcal. in 1 M solution. Thus for the reaction



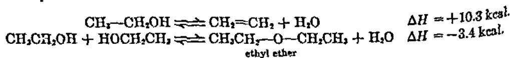
$$C_2H_5OH + HBr \rightleftharpoons C_2H_5Br + H_2O$$

ΔF is -7.6 kcal., starting with anhydrous materials, and $+7.6$ kcal., starting with 1 M solutions in water. The equilibrium therefore in the former case lies well on the side of the alkyl bromide and in the latter case well on the side of the alcohol.

The position of equilibrium is intermediate between the two extremes when the amount of water is intermediate. In a saturated aqueous solution of hydrobromic acid, ΔF of formation of HBr has the same value as that of the gas. Thus a saturated aqueous solution of hydrobromic acid is a satisfactory reagent, for the equilibrium is not greatly different from the equilibrium starting with anhydrous materials. The reaction actually proceeds faster, because of the catalytic effect of water. Reactions of hydrogen iodide and hydrogen chloride are affected similarly.

In actual preparations it is not necessary that the conditions be those under which the equilibrium constant is near the maximum value, since the product usually can be distilled away from the reactants, thus allowing one or both reactants to disappear.

6. *Alkene formation and ether formation.* Alcohols may lose water in two different ways: one mole of water from one mole of alcohol to produce an olefin; one mole of water from two moles of alcohol to produce an ether. Methanol can undergo only the second reaction. The reactions are described together since they proceed under similar conditions.



$$CH_3{-}CH_2OH \rightleftharpoons CH_2{=}CH_2 + H_2O \qquad \Delta H = +10.3 \text{ kcal.}$$
$$CH_3CH_2OH + HOCH_2CH_3 \rightleftharpoons \underset{\text{ethyl ether}}{CH_3CH_2{-}O{-}CH_2CH_3} + H_2O \qquad \Delta H = -3.4 \text{ kcal.}$$

For the gas phase reactions at 25°, if they could take place, ΔH values from heat of combustion data are +10.3 kcal. for the olefin and −3.4 kcal. for the ether reaction. The olefin reaction is endothermic, the ether reaction exothermic. The ΔF values for the reactions with the compounds in their normal states are +1.4 kcal. and −2.8 kcal., respectively. Thus equilibrium conditions at 25° are on the side of alcohol in the first reaction, and on the side of ether in the second reaction, but no reaction takes place in either case because the rate is very low. As the temperature is raised in order to obtain any reaction, the position of equilibrium will shift, the ethylene reaction to favor ethylene, the ether reaction to favor alcohol. In the gaseous ethylene reaction the equilibrium constant, K_1, has a value not far from unity at about 70° and gradually increases with a rise in temperature, being 60 at 200°. In the gaseous ether reaction, the equilibrium constant, K_2, has a value not far from unity at 350° and continues to decrease with further rise in temperature.

$$K_1 = \frac{[C_2H_4][H_2O]}{[C_2H_5OH]}$$

$$K_2 = \frac{[C_2H_5OC_2H_5][H_2O]}{[C_2H_5OH]^2}$$

Best catalysts for these reactions are strong acids, for example, sulfuric acid. When ethyl alcohol and sulfuric acid are heated, the ether reaction becomes significant at about 125°, and the olefin reaction at about 145°. Since both ethyl ether and ethylene are more volatile than ethyl alcohol, they can be distilled away from the liquid reaction mixture at these temperatures. In order to attain a temperature of 145° in the liquid phase, the ratio of acid to alcohol must be higher for olefin formation than for ether formation. Similar relationships hold for higher alcohols, except that the respective temperatures are somewhat lower. For example, in the case of n-butyl alcohol it is possible for the ether reaction to be significant at 110° with an amount of sulfuric acid which does not cause olefin formation until about 140°. Ethers of higher alcohols (butyl and higher) boil higher than the alcohols, whereas the corresponding olefins boil lower. Thus it usually is easier to convert a higher alcohol to an olefin than to an ether, since it is necessary only to add enough sulfuric acid to promote formation of the olefin, and distil this away as it is being formed.

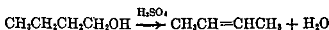
The relative rates of olefin formation are in the order: tertiary > secondary > primary. A tertiary alcohol yields the olefin when heated with a relatively weak acid such as oxalic acid. Thus it is difficult to obtain ethers of tertiary alcohols, because of the tendency to form the olefin instead. Ethers of secondary alcohols can be prepared by careful control of conditions.

Other catalysts are the typical solid dehydrating catalysts. Among these are aluminum oxide, thorium oxide, siliceous earth, and anhydrous aluminum sulfate. These are not so effective as sulfuric acid. A higher temperature is necessary. Alcohol vapor is passed over the catalyst at elevated temperatures, and an equilibrium is set up between the alcohol and the products.

From ethyl alcohol, ether is formed first. With aluminum oxide, ether formation starts at about 220° and proceeds well at about 300°. However, at this temperature ethylene formation becomes important and at 350° usually is the main reaction. As the temperature is raised above 300°, the equilibrium conditions favor ethylene formation at the expense of ether formation (refer to ΔH, above). This explains why ether formation takes place over a limited range of temperature, and above this olefin formation is the main reaction.

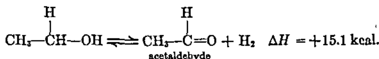
Lowering the pressure favors olefin formation, and raising the pressure favors ether formation, because of the volume relationships in the reactions.

When olefins are prepared from higher alcohols, the product is not always the expected olefin, especially when the catalyst is acidic. Thus the butene obtained from 1-butanol, as well as from 2-butanol, with sulfuric acid is 2-butene.

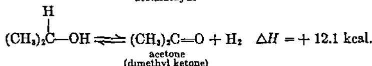


$$CH_3CH_2CH_2CH_2OH \xrightarrow{H_2SO_4} CH_3CH{=}CHCH_3 + H_2O$$

7. *Dehydrogenation.* Alcohols, like hydrocarbons, lose hydrogen at elevated temperatures. The dehydrogenation of primary and secondary alcohols is catalyzed by metals, of which copper, silver, or a copper-silver alloy are especially effective, the latter allowing the reaction to proceed slowly at temperatures near 200°. Usually the temperature is 300° or higher. The products are respectively aldehydes and ketones.



$$CH_3{-}CH_2{-}OH \rightleftharpoons \underset{\text{acetaldehyde}}{CH_3{-}CH{=}O} + H_2 \quad \Delta H = +15.1 \text{ kcal.}$$



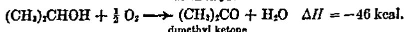
$$(CH_3)_2CH{-}OH \rightleftharpoons \underset{\text{acetone (dimethyl ketone)}}{(CH_3)_2C{=}O} + H_2 \quad \Delta H = +12.1 \text{ kcal.}$$

Important deductions can be drawn from the thermodynamic data. If reaction could take place at 25°, the equilibrium would lie far to the left, for ΔF also is positive (refer to p. 24). Actually ΔF for the second reaction in the gas phase at 25° is about +6 kcal. The equilibrium conditions favor a primary alcohol more than a secondary alcohol. A rise in temperature brings about a shift in the position of equilibrium. At a temperature of about 210° the equilibrium constant is unity in the case of isopropyl alcohol. Dehydrogenation of an alcohol takes place at a lower temperature than the dehydrogenation of an alkane to an alkene, for this requires the absorption of about 30 kcal.

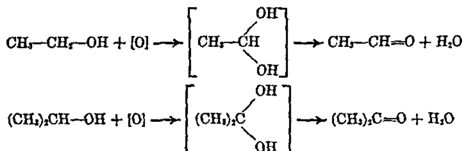
8. *Oxidation.* Oxygen oxidizes alcohols to carbon dioxide and water in flame combustion. Heats of combustion have been determined accurately for a number of alcohols (Table 38, p. 139). Oxygen can also effect partial oxidation of primary alcohols to aldehydes (and acids) and of secondary alcohols to ketones. This is accomplished by passing the alcohol with the proper amount of oxygen or air through a hot reaction zone containing a dehydrogenating

catalyst. Under these conditions the reaction is highly exothermic, owing to the high heat of combustion of hydrogen, *viz.*, 68.3 kcal. (p. 57). The values below are calculated from bond energies.





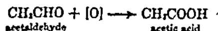
Oxidation of alcohols in the laboratory usually is carried out in aqueous solution by means of dichromic acid, usually called "chromic acid mixture" (a dichromate plus aqueous sulfuric acid). The reactions are strongly exothermic. Primary alcohols are oxidized to aldehydes, secondary to ketones. In the equations below, [O] represents oxygen supplied by the oxidizing agent.



Oxidation is believed to involve **hydroxylation,** *i.e.*, the conversion of a hydrogen atom to the hydroxyl radical. This takes place more readily if a hydroxyl radical already is attached to the carbon atom to which the hydrogen atom is attached. The compound so formed is not stable, a condition indicated by the brackets above, for it spontaneously loses a molecule of water. Very few stable organic compounds are known in which two hydroxyl groups are attached to one carbon atom (however, see Chloral, Chap. 17). The oxidation product from a primary alcohol is an aldehyde, and from a secondary alcohol is a ketone.

A tertiary alcohol is not oxidized as easily as a primary or secondary alcohol. This is due to the fact that there is no hydrogen atom attached to the carbon atom holding the hydroxyl group. For example, tertiary butyl alcohol, $(CH_3)_3COH$, is not attacked by dilute dichromic acid. Since the oxidizing power of dichromate increases as the sulfuric acid is made more concentrated, *i.e.*, as the ratio of acid-to-water is increased, a point is finally reached where the tertiary alcohol is oxidized. When this happens, oxidation has been initiated on another carbon atom, and once started it proceeds rapidly with a breaking of the carbon chain and the formation of compounds having fewer carbon atoms, *viz.*, acetone, acetic, formic, and carbonic acids.

When a primary alcohol is oxidized by dichromic acid, the oxidation does not stop at the aldehyde stage, since the aldehyde also is oxidized. The final product is an acid (Chap. 12).



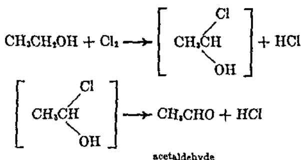
Thus a primary alcohol may be converted to either the corresponding aldehyde or the acid, depending upon the experimental conditions.

Primary and secondary alcohols are oxidized by other reagents, for example, potassium permanganate. This can be used under either basic or acidic conditions. *Under alkaline conditions at room temperature a primary alcohol is oxidized to the corresponding acid.* The expected product, an aldehyde, is rapidly oxidized to the acid under these conditions.



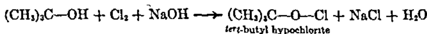
A secondary alcohol under alkaline conditions is cleaved to compounds (mainly acids) of fewer carbon atoms. The expected product, a ketone, is cleaved this way under these conditions (Chap. 17). In cold, aqueous sulfuric acid a primary alcohol is oxidized to the aldehyde, and a secondary to the ketone Under neutral conditions primary and secondary alcohols are only very slowly oxidized by aqueous permanganate at room temperature.

9 *Halogenation.* Alcohols, like hydrocarbons, undergo substitution with chlorine and bromine. Sometimes various products are formed, but in general the point of easiest substitution is on the carbon atom holding the hydroxyl radical. Thus primary and secondary alcohols react much more easily than tertiary. The resulting halogenated alcohol is unstable, indicated by enclosure in brackets in the case below, and easily loses hydrogen halide.



Thus primary alcohols are converted to aldehydes, secondary to ketones. The reaction is essentially an oxidation of the alcohol by the halogen. Other reactions take place (see Chloral, Chap. 17). Tertiary butyl alcohol, since it is only slowly attacked, sometimes is used as a solvent for bromine during the bromination of other compounds. The inability of iodine to react is shown by the use of a solution of iodine in alcohol, tincture of iodine, as an antiseptic. When water is present, chlorine or bromine can act as an oxidizing agent and cause oxidation of a primary or secondary alcohol.

A tertiary alcohol with chlorine under basic conditions sometimes yields a hypochlorite, as in the case of *tert*-butyl alcohol.



The product is an unstable, reactive compound. It liberates iodine from hydriodic acid and oxidizes many organic compounds.

Balancing Oxidation-Reduction Equations. One method involves the following steps: determining the number of atoms of oxygen needed to change the original *substance to the product, as in the simplified equations above; writing an equation* for the hypothetical decomposition of the oxidizing agent to yield oxygen, under the experimental conditions; and equating oxygen consumed with oxygen available. The oxidation of ethyl alcohol by dichromate under acid conditions is a typical example.

$$3\{CH_3CH_2OH + [O] \longrightarrow CH_3CHO + H_2O\}$$
$$K_2Cr_2O_7 + 5\,H_2SO_4 \longrightarrow 2\,KHSO_4 + Cr_2(SO_4)_3 + 4\,H_2O + 3\,[O]$$
$$\overline{3\,CH_3CH_2OH + K_2Cr_2O_7 + 5\,H_2SO_4 \longrightarrow 3\,CH_3CHO + 2\,KHSO_4 + Cr_2(SO_4)_3 + 7\,H_2O}$$

Another method is based upon assigning different oxidation numbers to carbon, corresponding to its different oxidation states, *viz.*, methane, IV, methanol, V, formaldehyde, VI, formic acid, VII, and carbonic acid (or carbon dioxide), VIII.

```
   H            H
   +            +
   -            -
H+-C-+H     H+-C-+H     H+-C-+H     H+-C+-OH     HO-+C+-OH
   -            +          ++           ++           ++
   +            -          --           --           --
   H            OH         O            O            O
   IV           V          VI           VII          VIII
```

Hydrogen is considered positive, hydroxyl negative, and oxygen doubly negative. Thus the oxidation numbers of carbon, from the completely reduced stage to the completely oxidized stage are: −4 in IV, −2 in V, 0 in VI, +2 in VII, and +4 in VIII. A similar sequence holds in the series of chlorinated compounds from methane, IV, through methyl chloride, IX, methylene chloride, X, and chloroform, XI, to carbon tetrachloride, XII. Here the chlorine is considered to have a negative charge.

```
   H            H            Cl           Cl           Cl
   +            +            -            -            -
   -            -            +            +            +
H+-C-+H     H+-C-+H     H+-C-+H     H+-C+-Cl     Cl-+C+-Cl
   -            +            +            +            +
   +            -            -            -            -
   H            Cl           Cl           Cl           Cl
   IV           IX           X            XI           XII
```

The oxidation number of carbon increases by two when passing from one oxidation stage to the next higher stage. Thus one atom of oxygen or one molecule of chlorine theoretically is required. This increase of two is therefore associated with the oxidation of any primary alcohol to an aldehyde, or of any secondary alcohol to a ketone. To balance an oxidation-reduction equation in which organic compounds are involved, *it is necessary first to balance the charges involved in the oxidation and reduction, and* then to take the proper amount of nonoxidizing and nonreducing reagents. Since one chromium atom is reduced three steps from +6 to +3, and carbon is oxidized two steps, from −2 to 0, the ratio of $K_2Cr_2O_7$ to C_2H_5OH is 1 to 3. (Numbers located above the atoms and representing oxidation states are circled.)

$$\overset{(+6)}{Cr_2}O_7 + 3\,CH_3\overset{(-2)}{C}H{<}^{H}_{OH} \longrightarrow 2\overset{(+3)}{Cr} + 3\,CH_3\overset{(0)}{C}H{=}O$$

On the left are six plus charges (+12, −6) and on the right are six also (+6, 0). Charges of ions need not be balanced at this point. A sufficient number of protons are taken to form water, in order to balance the number of oxygen and hydrogen atoms, as well as ionic charges. Of the two methods described above the one based on oxidation numbers has the disadvantage that there may be confusion with formal charges. For this reason the method of equating oxygen available with oxygen needed is recommended.

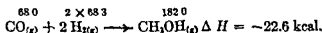
INDIVIDUAL ALCOHOLS

Methanol, Methyl Alcohol, CH_3OH. For many years the principal source of this alcohol was wood distillation so-called, actually the pyrogenic decomposition of wood. The liquid which is condensed out of the gaseous products consists of a water phase, called **pyroligneous acid**, and an oily tarry phase. The aqueous phase contains 1 to 2 per cent of methanol, 9 to 10 per cent of acetic acid, 0.1 to 0.5 per cent of acetone, and smaller amounts of other compounds. Methanol and acetone are then fractionally distilled from the solution. After removal of water from the distillate by treatment with lime, another fractional distillation yields methanol of 95 per cent purity, the impurity being mainly acetone, which with the other impurities imparts a disagreeable odor to the product. This is the **wood alcohol** of commerce, which in this form is largely used as a denaturant for ethyl alcohol. By careful fractional distillation pure methanol may be obtained.

Synthetic methanol is now produced in large quantity by the reduction of carbon monoxide with hydrogen in the presence of special catalysts at high temperatures and pressures. The gas phase reaction, if it could be carried out at 25°, would be exothermic, for ΔH calculated from heats of combustion is −22 6 kcal.

$$\overset{68\,0}{CO_{(g)}} + \overset{2 \times 68\,3}{2\,H_{2(g)}} \longrightarrow \overset{182\,0}{CH_3OH_{(g)}}\ \Delta H = -22.6 \text{ kcal.}$$

The catalyst usually contains metallic copper and the oxide of some other metal, for example, chromium, manganese, molybdenum, titanium, or zinc. A very effective one is a mixture of the oxides of copper, zinc, and chromium in the molal ratio of 49:43:8. Using catalysts of this type, the reduction for the most part stops at the methanol stage, but a small amount is reduced to methane. It will be recalled that when nickel is the catalyst, carbon monoxide is easily reduced to methane (p. 40). Side reactions with the copper catalysts may lead to the formation of some of the higher alcohols.



nent that only a trace of methanol is in equilibrium with carbon monoxide and hydrogen. But by increasing the pressure on the system the reaction is driven forward. In actual practice, therefore, a mixture of hydrogen and carbon monoxide under a pressure of 100 atmospheres or more is passed over a suitable catalyst at 250 to 350°, the methanol is condensed out, and the residual gas, along with more carbon monoxide and hydrogen, is circulated through the apparatus again. Finally after the methane concentration has built up, the gas is discarded, and the cycle started anew. The product resulting from this process is purer than that obtained by wood distillation but may contain some higher alcohols. It is called synthetic methanol. Since it is

desirable to restrict as much as possible the use of the word alcohol to ethyl alcohol alone, this text will conform to present-day usage by referring to this compound from now on as methanol, not methyl alcohol.

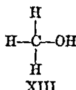
Methanol is used commercially as a solvent for shellac, gums, etc., as an intermediate in the preparation of certain dyes, for the preparation of formaldehyde, and for other purposes. Methanol is poisonous and causes blindness when taken internally or when one is repeatedly exposed to the vapor mixed with air.

Structure of Methanol. By the reaction of methyl chloride with silver hydroxide, silver chloride and methanol are produced.



$$CH_3Cl + AgOH \longrightarrow CH_3OH + AgCl$$

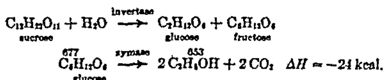
The hydroxyl radical has taken the place of the chlorine atom, and the molecule of methanol therefore contains both methyl and hydroxyl radicals because a methyl radical was present in the halide. This leads to the structure shown by XIII.



XIII

This can be the only possible structure if the atoms have their usual valence, four for carbon, two for oxygen, and one for hydrogen. Moreover, chemical behavior with metals shows that one hydrogen atom is combined differently from the other three, since it is possible to obtain a monosodium salt of methanol, sodium methoxide, CH_3ONa, but not a disodium salt. These properties are satisfactorily represented by XIII.

Ethyl Alcohol, Ethanol, C_2H_5OH. Dilute solutions of alcohol have been known from the earliest times, since alcohol is present in the wine formed by the fermentation of fruit juices, especially that of the grape. Alcohol is produced in large quantities by yeast fermentation of liquids containing the simple sugars, glucose (grape sugar) and fructose (fruit sugar), $C_6H_{12}O_6$, or of carbohydrate material which can be readily converted into one or both of these, such as sucrose (cane sugar) $C_{12}H_{22}O_{11}$, starches $(C_6H_{10}O_5)_n$, or cellulose $(C_6H_{10}O_5)_n$ (see Yeast Fermentation, Chap. 42). The fermentation reaction of glucose is exothermic, for ΔH calculated from heats of combustion, and neglecting heats of dilution, is −24 kcal.



$$\underset{\text{sucrose}}{C_{12}H_{22}O_{11}} + H_2O \xrightarrow{\text{invertase}} \underset{\text{glucose}}{C_6H_{12}O_6} + \underset{\text{fructose}}{C_6H_{12}O_6}$$

$$\underset{\text{glucose}}{\overset{677}{C_6H_{12}O_6}} \xrightarrow{\text{zymase}} 2\,\overset{653}{C_2H_5OH} + 2\,CO_2 \quad \Delta H = -24 \text{ kcal.}$$

Fermentation proceeds best in a solution containing about 10 per cent of sugar. When the alcohol concentration reaches about 12 per cent, the yeast is usually killed, but fermentation may continue, provided sugar is present, up to about 15 per cent. Here the zymase is precipitated and action ceases, even though additional sugar is present. Rarely does the alcoholic content from fermentation alone exceed 18 per cent.

When grains are the starting material, the fermented liquid contains, besides water, ethyl alcohol, and yeast cells, other materials in smaller amounts, such as higher

alcohols, acids, and glycerol. Separation is effected by means of efficient fractionating columns to give in one operation alcohol of 96 per cent by volume (the constant boiling mixture with water distils at 78.15° and contains 95.57 per cent alcohol by weight, 97.20 per cent by volume). The higher alcohols sometimes are obtained as a separate fraction, called fusel oil. The main constituent of this is isoamyl alcohol (see Higher Alcohols) Rectified alcohol of 94 to 96 per cent is known as neutral spirits and Cologne spirits.

The addition of solid potassium carbonate to an aqueous solution of alcohol which is not too dilute causes the alcohol to separate as a second liquid phase with 9 or 10 per cent of water dissolved in it.

Absolute alcohol, or alcohol from which all but a fraction of a per cent of water has been removed, is made by boiling the 96 per cent alcohol with quicklime, which combines with water but not with alcohol. The product usually contains about 0.5 per cent water It does not color anhydrous copper sulfate blue, as 96 per cent alcohol does, and dissolves barium oxide with the production of a yellow color, which the other alcohol does not do. Absolute alcohol is miscible with gasoline.

Uses of Ethyl Alcohol. Ethyl alcohol is an important industrial substance. Aside from its presence in alcoholic beverages it finds extensive application as a solvent, as for example, in paints, lacquers, varnishes, pharmaceutical preparations (*tinctures*), flavoring extracts, and perfumes. From it are manufactured many other organic compounds, for example, ether, acetic acid, ethyl acetate, and other ethyl *esters*. It is used as a fuel. The so-called **solid alcohol** is alcohol (denatured) in which a small amount of a suitable substance has been dissolved hot. On cooling this causes a gel to form. Calcium acetate, soaps, or nitrocellulose can be used.

Denatured Alcohol. The manufacture of alcohol in any form in the United States is under strict federal control because of the high excise tax which must be paid on alcohol not denatured. During World War II the tax on distilled spirits was $9.00 per proof gallon, according to the Revenue Act of 1943. This was raised to $10.50 per proof gallon in 1951. For industrial purposes alcohol can be denatured, that is, rendered unfit for beverage purposes, by the addition of poisonous or disagreeable substances. A common denaturant is wood alcohol. Pyridine often is added on account of the disagreeable odor. About eighty different denaturing formulas are legal and allow alcohol to be sold and used tax free. Alcohol used for medicinal or scientific purposes is tax exempt when the user guarantees compliance with the regulations. In the United States a proof gallon is one containing 50 per cent of alcohol by volume. The manufacture and sale of alcohol is under strict government control in most foreign countries also.

Alcoholic Beverages. There are two types of alcoholic beverages, undistilled and distilled. The principal undistilled beverages are beer, champagne, and wine. Undistilled beverages have a much lower alcohol content than the distilled; among the latter are whiskey, gin, rum, and brandy.

Beer is manufactured by fermenting malted grain. It usually contains 3 to 5 per cent alcohol. Addition of hops imparts a bitter taste.

Wine and champagne are fermented grape juice. In order to improve the flavor a good wine is stored for years. The alcoholic content resulting from the sugars present in the grape juice may rise to 15 per cent, but usually is 8 to 12 per cent. Some wines contain as much as 22 per cent alcohol. Usually a wine having an alcoholic content of 18 per cent or higher is fortified, that is, alcohol has been added. Typical unfortified wines are claret, Rhine wines, sauterne, and burgundy. Typical fortified

time a gas which contains 55 per cent carbon dioxide and 45 per cent hydrogen. After a part of the carbon dioxide has been removed, the resulting gas, having the proper proportion of carbon dioxide and hydrogen, is converted into methanol by high pres-

TABLE 40 | **Physical Constants of Some Higher Alcohols**

NAME	RADICAL	M.P. °C	B.P. °C	SP. GR. 20/4	SOLY. IN WATER G./100 G.	DIEL. CONST.
n-Propyl	$CH_3CH_2CH_2$—	−127	97.8	0 804	misc.	22
Isopropyl	$(CH_3)_2CH$—	−86	82 5	.789	misc.	26
n-Butyl	$CH_3(CH_2)_3$—	−80	117.7	.810	7.9	19
Isobutyl	$(CH_3)_2CHCH_2$—	−108	107.9	.802	10.0	19
sec-Butyl	$C_2H_5CH_3CH$—	−114	99.5	.806	12.5	15
tert-Butyl	$(CH_3)_3C$—	25.5	82.9	.789	misc.	11
n-Amyl	$CH_3(CH_2)_4$—		137.9	.817	2 3	16
Isoamyl	$(CH_3)_2CH(CH_2)_2$—	−117	132	.813	2	15
Active amyl	$C_2H_5CH_3CHCH_2$—		128	.816	3.6	
tert-Amyl	$C_2H_5(CH_3)_2C$—	−12	102	.809		12

sure synthesis. The butanol now finds extensive use, mainly in the form of esters, especially the acetate, as a solvent for numerous purposes. This fermentation process was originally developed during World War I as a source of acetone, which was in great demand since it was used in the manufacture of the official British explosive, cordite. Thousands of gallons of butanol were produced as a by-product and were stored in large reservoirs for four or five years while a use was being sought for it. Synthetic 1-butanol from butane is supplanting fermentation butanol.

Tertiary butyl alcohol is interesting in that it is miscible with water in all proportions and is a good solvent, not only for many organic compounds, but also for some inorganic. Because it is not as easily oxidized or brominated as primary or secondary alcohols, it may be used as a solvent for chromic anhydride or for bromine when it is desired to oxidize or brominate other compounds. It reacts rapidly with aqueous hydrochloric, hydrobromic, or hydriodic acid to form the corresponding halide.

Amyl Alcohols, Pentanols, $C_5H_{11}OH$. There are eight structurally isomeric amyl alcohols predicted by theory and just eight are known, three derived from *n*-pentane, four from isopentane, and one from neopentane. Some of them are listed in Table 40. Isoamyl alcohol is the best known of these for it is the most important constituent of fusel oil.

Identification of Alcohols. Alcohols dissolve in concentrated sulfuric acid. This is a property shown by compounds of not too complicated structure when they contain oxygen and therefore is not a conclusive test for an alcohol.

Alcohols evolve hydrogen with metallic sodium. Since the rate is slower with higher alcohols, it may be necessary to heat. It is desirable to note that water as an impurity in some other compound which itself has no action upon the metal, will evolve hydrogen when sodium is added. Other compounds,

among them acids, phenols, mercaptans, esters, etc., also evolve hydrogen when sodium is added. The test although not conclusive for alcohols is, however, *a useful one.*

Primary and secondary alcohols evolve hydrogen chloride on the addition of acetyl chloride and are converted into esters of acetic acid. However, this is not a conclusive test since other compounds, phenols, for example, react similarly; moreover, tertiary alcohols yield the corresponding tertiary chloride, not hydrogen chloride.

Alcohols react when heated with concentrated hydrobromic acid to form volatile alkyl bromides heavier than water. This is a useful test for alcohols in general since they will all give bromides insoluble in and heavier than water.

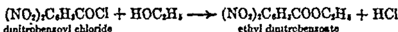
The lower primary, secondary, and tertiary alcohols may be distinguished by the following reactions. The tertiary alcohols react very rapidly with concentrated hydrochloric acid at the ordinary temperature to form chlorides insoluble in the acid. The tertiary alcohols also react very rapidly and the secondary alcohols within several minutes at the ordinary temperature with concentrated hydrochloric acid saturated with zinc chloride, forming insoluble liquid chlorides. The primary alcohols, on the other hand, react with neither reagent at room temperature. However, they react when heated with the hydrochloric acid–zinc chloride reagent, forming volatile chlorides lighter than water.

The lower primary, secondary, and tertiary alcohols formerly were distinguished by means of the red, white, and blue reaction of nitroparaffins (Chaps. 8, 24).



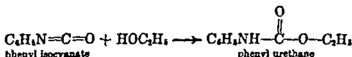
$$ROH \xrightarrow{HBr} RBr \xrightarrow{AgNO_2} RNO_2$$

Individual alcohols may be identified by conversion to solid derivatives by the reaction with acid chlorides of high molecular weight, for example, dinitrobenzoyl chloride, $(NO_2)_2C_6H_3COCl$.



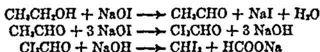
$$\underset{\text{dinitrobenzoyl chloride}}{(NO_2)_2C_6H_3COCl} + HOC_2H_5 \longrightarrow \underset{\text{ethyl dinitrobenzoate}}{(NO_2)_2C_6H_3COOC_2H_5} + HCl$$

They also give solid urethanes with phenyl isocyanate.



$$\underset{\text{phenyl isocyanate}}{C_6H_5N{=}C{=}O} + HOC_2H_5 \longrightarrow \underset{\text{phenyl urethane}}{C_6H_5NH{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}O{-}C_2H_5}$$

Iodoform Test. Ethyl alcohol when heated with aqueous sodium carbonate (or hydroxide) and aqueous potassium iodide containing dissolved iodine forms iodoform, the reaction proceeding in three steps (Chap. 17).



$$CH_3CH_2OH + NaOI \longrightarrow CH_3CHO + NaI + H_2O$$
$$CH_3CHO + 3\,NaOI \longrightarrow CI_3CHO + 3\,NaOH$$
$$CI_3CHO + NaOH \longrightarrow CHI_3 + HCOONa$$

The iodoform is identified by its characteristic appearance and odor. Other alcohols containing the grouping CH_3CHOH also give the iodoform test. Thus isopropyl alcohol does, but normal propyl does not.

PROBLEMS

1. Name the following according to the I.U.C. system and, if possible, as a derivative of methanol and as an alcohol. Classify as primary, secondary, or tertiary.

a) $CH_3CHOHCH_2CH_2CH_3$
b) $CH_3CHOHCH_2CH_2CH_2CH_3$
c) $(CH_3)_3CCHOHCH_3$
d) $(CH_3)_2CHCOH(CH_3)_2$
e) $CH_3CH_2CH(CH_3)CHOHCH_3$
f) $(CH_3)_2CHCH_2CH_2CH_2CH_2OH$
g) $(CH_3)_3CCH_2CHOHCH_3$
h) $(CH_3)_2CHC(CH_3)_2CH_2OH$
i) $CH_3CH_2CH(CH_3)C(CH_3)_2OH$
j) $(CH_3)_2CHCH_2CHOHCH_2CH_3$
k) [illegible]
l) [illegible]
m) [illegible]
n) $(CH_3)_2CHCH(CH_3)CH(CH_3)CH_2OH$

2. Outline the steps involved (arrow, reagent, and conditions are sufficient) when obtaining 1-propanol from:

a) 1-chloropropane
b) *n*-propyl acetate
c) ethyl alcohol
d) methyl alcohol
e) propionaldehyde

3. Show the steps involved in a practical laboratory preparation of the following, *from* compounds of fewer carbon atoms:

a) 2-butanol
b) 2-pentanol
c) 3-pentanol
d) 2-methyl-1-butanol
e) 3-methyl-2-butanol
f) 2-methyl-2-butanol
g) 2-hexanol
h) 1-hexanol
i) 3-hexanol
j) 4-methyl-2-pentanol
k) 2-methyl-3-pentanol
l) 2-methyl-2-pentanol
m) 3-methyl-3-pentanol
n) 3-ethyl-3-pentanol

4. Write the structure of an alkene which will yield the following, reasonably free of isomeric forms:

a) 2-propanol
b) 2-butanol
c) 2-methyl-2-propanol
d) 2-methyl-2-butanol
e) 3-methyl-2-butanol
f) 3-methyl-3-pentanol
g) 2-pentanol
h) 3-hexanol

5. Write balanced equations with the actual reagents for the reactions involved in a practical laboratory preparation of the following from *n*-propyl alcohol:

a) lithium propoxide
b) aluminum propoxide
c) *n*-propyl bromide
d) *n*-propyl cyanide
e) *n*-propyl iodide
f) *n*-propyl acetate
g) propionaldehyde
h) propane
i) *n*-propyl chloride
j) *n*-propyl sulfide
k) propionic acid
l) *n*-amyl bromide
m) *n*-propylmercuric bromide
n) 1-pentyne
o) 1-pentene
p) 1-hexene

6. Write balanced equations with the actual reagents for the reactions involved when 2-butanol reacts with the following:

a) ethyl magnesium bromide
b) ethyllithium
c) hydrogen bromide (cold)
d) hydrobromic acid (heated)
e) phosphorus trichloride
f) acetyl chloride
g) dichromic acid
h) sulfuric acid (warm)
i) sulfuric acid (refluxed)
j) metallic calcium
k) sodium acetylide
l) sodium hexynide

7. Describe a convenient and reasonably rapid chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish.

a) ethyl alcohol from ethyl iodide
b) ethanol from 1-butanol
c) 1-butanol from 2-butanol
d) isopropyl from *tert*-butyl alcohol
e) *n*-propyl from *sec*-butyl alcohol
f) isopropyl from isobutyl alcohol
g) ethanol from 2-propanol
h) ethanol from 1-hexene
i) ethanol from 1-hexyne
j) ethanol from *n*-hexane
k) isoamyl from *tert*-amyl alcohol
l) 1-pentanol from 2-pentanol

8. It is desirable to effect an essentially quantitative separation of the two compounds below from each other, so as to obtain one reasonably pure and free of the other. State the method you would employ, specifying reagent, conditions, and solvent, if any.

a) methanol and 1-hexene
b) ethanol and tetramethylethylene
c) methanol and 1-bromopropane
d) ethanol and 1-chlorobutane
e) 1-propanol and 1-chloropentane
f) active amyl alcohol and 1,3-dichloropropane

9. From the values of ΔF, page 145, calculate the approximate equilibrium constant for the hypothetical equilibrium at room temperature between:

a) ethyl alcohol and ethylene
b) ethyl alcohol and ethyl ether

CHAPTER 11

Dihydric and Trihydric Saturated Alcohols; Chlorohydrins; Unsaturated Alcohols

DIHYDRIC AND TRIHYDRIC ALCOHOLS

Dihydric alcohols usually are called glycols (Gr. *glykys*, sweet) from the simplest known member of the series, ethylene glycol, $CH_2OH—CH_2OH$, which has a sweet taste. Theoretically the simplest glycol should be methylene glycol, dihydroxymethane, $CH_2(OH)_2$, but this compound has not been isolated as such. In reality it is hydrated formaldehyde, CH_2O, and is known to be present in an aqueous solution of formaldehyde and in equilibrium with it (see Addition of Water, Chap. 17).



$$H_2C{=}O + H_2O \rightleftharpoons H_2C(OH)_2$$

Chemically then, methylene glycol acts as an aldehyde, not as a glycol. In general, compounds in which two hydroxyl groups are attached to one carbon atom are not stable, although there are a few apparent exceptions (see Chloral, Chap. 17). Chemically such compounds are aldehydes or ketones.

A glycol may be named as the glycol of a bivalent radical, for example, ethylene glycol, or as a dihydroxy alkane. In the I.U.C. system this is done by adding the suffix -diol to the name of the hydrocarbon, and indicating the position of the two hydroxyl groups by numbers. This method is easily extended to trihydric and polyhydric alcohols.

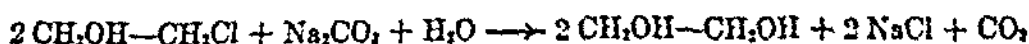
Ethylene Glycol, 1,2-Ethanediol, CH_2OHCH_2OH. This is a viscous, colorless liquid with a sweet taste. It is completely miscible with water and is strongly hygroscopic. It is essentially insoluble in hydrocarbon solvents, slightly soluble in ethyl ether (1 g./100 g.). Glycol has been used as an antifreeze in automobile radiators It and other glycols are important in the manufacture of a group of synthetic resins called the alkyd resins (Chap. 16). The methods of preparation described below for ethylene glycol are in general applicable to other glycols, except that (1) and (2) are not always satisfactory for secondary alcoholic groups, because of the tendency of secondary halogen compounds to undergo unsaturation.

1. *Hydrolysis of ethylene chloride or ethylene bromide.* This is done industrially by heating the chloride under pressure with aqueous carbonate at temperatures of 150 to 190°.

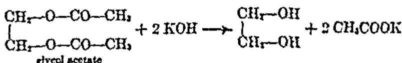


$$CH_2Cl—CH_2Cl + Na_2CO_3 + H_2O \longrightarrow CH_2OH—CH_2OH + 2\,NaCl + CO_2$$

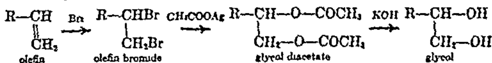
2. *Hydrolysis of ethylene chlorohydrin.* This may be accomplished by heating with water at 100°, more rapidly in the presence of a carbonate.



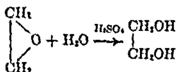
3. *Saponification of glycol esters,* by heating with a strong base.



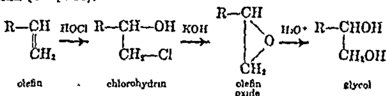
This is a useful general method, for the acetates can be obtained from the olefin bromides by the action of an inorganic acetate.



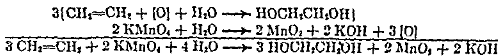
4. *Hydration of ethylene oxide.* This takes place readily in a dilute aqueous solution of a strong acid, which acts catalytically.



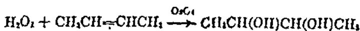
This is a convenient general method, and by it a glycol can be obtained conveniently from the olefin (Chap. 16).

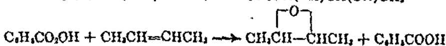


5. *Hydroxylation of ethylene.* This can be done with permanganate under neutral conditions. A magnesium salt (or other suitable salt) is added to buffer the solution, otherwise the glycol undergoes extensive oxidation under the alkaline conditions that develop.



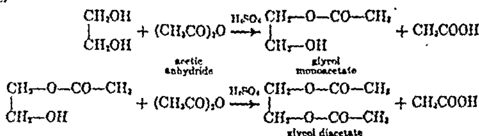
Other reagents that bring about hydroxylation are hydrogen peroxide in the presence of osmium tetroxide, and perbenzoic or other per acid. In the latter case the first step is the formation of an olefin oxide.



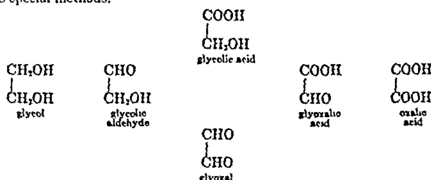


The oxide readily hydrates to a glycol in aqueous acid.

Reactions of Glycol. Glycol undergoes the typical reactions of alcohols, and each hydroxyl group may react independently of the other. This behavior is typical of other glycols, also. Thus it is possible to obtain both a monoacetate and a diacetate.



Also, different oxidation products may be obtained from glycol. Thus with cold nitric acid, glycolic acid is obtained, and with hot nitric acid, oxalic acid. Other oxidation products of glycol are known, in fact the compounds which are predicted by theory are all known, as shown below, but in general the preparation of most of these requires special methods.



Higher Glycols. *In Table 41 are names and physical properties of some glycols.* Compared to the corresponding monohydric alcohols they are less soluble in nonpolar

TABLE 41 | Some Glycols

NAME		FORMULA	M.P. °C	B.P. °C
I.U.C.	glycol			
1,2-Ethanediol	Ethylene	CH_2OHCH_2OH	−15.6	197.2
1,2-Propanediol	Propylene	$CH_3CHOHCH_2OH$		187.4
1,3-Propanediol	Trimethylene	$CH_2OHCH_2CH_2OH$		214 7
1,2-Butanediol	α-Butylene	$CH_3CH_2CHOHCH_2OH$		192
1,3-Butanediol		$CH_3CHOHCH_2CH_2OH$		208
2,3-Butanediol	β-Butylene	$CH_3CHOHCHOHCH_3$	34.4 [a]	182.5
2-Methylpropane-1,2-diol	Isobutylene	$(CH_3)_2COHCH_2OH$		178 6
1,4-Butanediol	Tetramethylene	$CH_2OHCH_2CH_2CH_2OH$	16	230

[a] Meso form.

solvents, such as the hydrocarbons, and more soluble in water. All of those listed are miscible with water in all proportions. Even in the case of solid 2,3-butanediol, as water is added the melting point drops, until soon the mixture is a liquid.

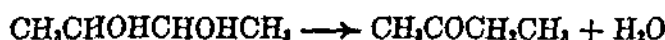
The butanediols are important in connection with butadiene. The production of 1,3-butanediol by the reduction of aldol (Chap. 17) was perfected about 1910. Recently 1,4-butanediol has become available from tetrahydrofuran (Chap. 44) and 2,3-butanediol through special fermentation methods. Cane sugar gives good yields of 2,3-butanediol with bacteria of the genus *Aerobacter*. Glucose and maltose undergo fermentation with *Aerobacter aerogens* with production of this glycol. Starch is fermented by *Aerobacillus polymyxa* One of the methods by which sugars, starch, and cellulose (Chap. 43) are converted to butadiene is through the intermediate formation of 2,3-butanediol.

1,3-Butanediol at a sufficiently high temperature (200–500°) over a suitably dehydrating catalyst is converted to butadiene.



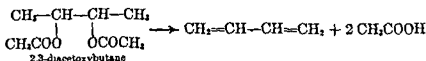
$$CH_3CHOHCH_2CH_2OH \longrightarrow CH_2{=}CH{-}CH{=}CH_2 + 2\,H_2O$$

However, 2,3-butanediol readily rearranges to butanone before dehydration to butadiene is effected.



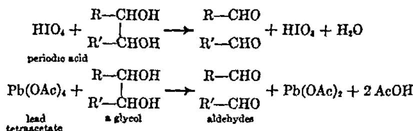
$$CH_3CHOHCHOHCH_3 \longrightarrow CH_3COCH_2CH_3 + H_2O$$

Decomposition to butadiene is realized, however, if the glycol is first converted to the diacetate, for this decomposes when heated sufficiently.



$$\underset{\text{2,3-diacetoxybutane}}{\begin{array}{c}CH_3{-}CH{-}CH{-}CH_3\\ \;\;|\qquad\;\; |\\ CH_3COO\quad OCOCH_3\end{array}} \longrightarrow CH_2{=}CH{-}CH{=}CH_2 + 2\,CH_3COOH$$

Scission of Glycols by Oxidation. Three oxidizing agents, *viz.*, periodic acid, lead tetraacetate, and sodium bismuthate, uniquely cleave glycols in which the hydroxyl groups are attached to adjacent carbon atoms. The carbon-to-carbon bond between hydroxyl groups is broken by the utilization of two equivalents of oxidizing agent, and two molecules of aldehyde are formed.



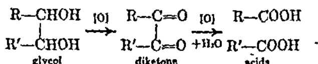
$$\underset{\text{periodic acid}}{HIO_4} + \begin{array}{c}R{-}CHOH\\ |\\ R'{-}CHOH\end{array} \longrightarrow \begin{array}{c}R{-}CHO\\ R'{-}CHO\end{array} + HIO_3 + H_2O$$

$$\underset{\text{lead tetraacetate}}{Pb(OAc)_4} + \underset{\text{a glycol}}{\begin{array}{c}R{-}CHOH\\ |\\ R'{-}CHOH\end{array}} \longrightarrow \underset{\text{aldehydes}}{\begin{array}{c}R{-}CHO\\ R'{-}CHO\end{array}} + Pb(OAc)_2 + 2\,AcOH$$

These reactions are useful in structural determinations, for the aldehydes either can be readily identified or can be oxidized to acids. The selection of the oxidizing agent usually depends upon the solubility behavior of the glycol, periodic acid (or sodium bismuthate) being used in aqueous solution, lead tetraacetate in nonaqueous (usually glacial acetic acid) solution. An advantage of periodic acid is detection of a reaction product (iodic acid) by the addition of silver ion under acid condition with precipitation of silver iodate.

Permanganate in excess cleaves glycols to acids. The oxidation is believed

to proceed in steps through the corresponding diketone, which in general is easily oxidizable to two molecules of acid.



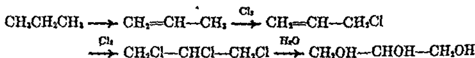
$$\begin{matrix} R-CHOH \\ | \\ R'-CHOH \\ \text{glycol} \end{matrix} \xrightarrow{[O]} \begin{matrix} R-C=O \\ | \\ R'-C=O \\ \text{diketone} \end{matrix} \xrightarrow[+H_2O]{[O]} \begin{matrix} R-COOH \\ \\ R'-COOH \\ \text{acids} \end{matrix}$$

Chromic acid mixture usually acts similarly except that other products may result. Dilute nitric acid cleaves glycols oxidatively, but with this reagent either of the other two carbon-to-carbon bonds attached to the CHOH groups may be broken.

Glycerol, 1,2,3-Propanetriol, $C_3H_5(OH)_3$. The simplest trihydric alcohol, commonly called glycerin, is a viscous, sweet-tasting liquid (Gr. *glykys*, sweet). Its properties are shown in Table 42.

Glycerol occurs widely distributed in nature in combination with monocarboxylic acids as fats (see Chap. 16), and is a by-product in the manufacture of soaps from fats. For many decades this was the sole source of glycerol. In the alcoholic fermentation of sugar a small amount (about 3 per cent of the weight of the sugar) of glycerol is produced. This can be increased to about 35 per cent by the addition of sodium bisulfite. This process became important in Germany in World War I, even though it is somewhat expensive.

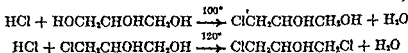
Recently in this country synthetic glycerol has become an important commercial product. The starting material is propane.



$$CH_3CH_2CH_3 \longrightarrow CH_2{=}CH{-}CH_3 \xrightarrow{Cl_2} CH_2{=}CH{-}CH_2Cl$$
$$\xrightarrow{Cl_2} CH_2Cl{-}CHCl{-}CH_2Cl \xrightarrow{H_2O} CH_2OH{-}CHOH{-}CH_2OH$$

Propylene (from propane by dehydrogenation) when chlorinated at a high temperature undergoes substitution to form allyl chloride (p. 72) and this at a lower temperature adds chlorine to form 1,2,3-trichloropropane. This undergoes hydrolysis at high temperatures to glycerol. Also, allyl chloride can be hydrolyzed to allyl alcohol and this can be converted to glycerol.

Reactions. One, two, or three of the hydroxyl groups of glycerol may react according to the usual reactions of alcohols, but usually with increasing difficulty. This is illustrated by the reactivity with hydrogen chloride, whereby glycerol monochlorohydrin, $CH_2ClCHOHCH_2OH$, and glycerol dichlorohydrin, $CH_2ClCHOHCH_2Cl$, are formed.



$$HCl + HOCH_2CHOHCH_2OH \xrightarrow{100^\circ} ClCH_2CHOHCH_2OH + H_2O$$
$$HCl + ClCH_2CHOHCH_2OH \xrightarrow{120^\circ} ClCH_2CHOHCH_2Cl + H_2O$$

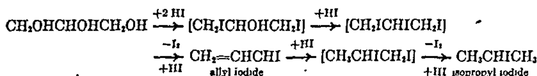
In order to replace the third hydroxyl group, a more vigorous reagent is needed.



$$PCl_3 + 3\ ClCH_2CHOHCH_2Cl \longrightarrow 3\ ClCH_2CHClCH_2Cl + P(OH)_3$$

Nitric acid (with concentrated sulfuric acid) forms glycerol trinitrate (nitroglycerin, Chap. 16).

Hydriodic acid reacts differently from other acids. With the proper amount of hydriodic acid the product is allyl iodide, but if the hydriodic acid is in large excess, the product is mainly isopropyl iodide.



The result is understandable on the basis that diiodides are unstable (p. 121) and that hydrogen iodide adds readily to the olefinic double bond (p. 70).

Glycerol is easily oxidized. When poured onto powdered potassium permanganate it ignites and burns with a blue flame. In aqueous solution glycerol is easily oxidized by a variety of oxidizing agents, most of which when present in excess cause scission of the first oxidation products with the formation of simpler substances, such as carbonic, formic, and oxalic acids. With cold dilute nitric acid or with dilute aqueous sodium hypochlorite containing a small amount of cobalt ion, a mixture of the corresponding aldehyde and ketone is obtained, namely, glyceric aldehyde, CH_2OH—CHOH—CHO and dihydroxyacetone, CH_2OH—CO—CH_2OH. With mercuric oxide suspended in aqueous sodium hydroxide, glycerol is oxidized to glyceric acid, CH_2OH—CHOH—COOH. Generally, however, complex mixtures of various oxidation products are obtained when glycerol is oxidized.

Uses. The principal uses of glycerol are in the manufacture of nitroglycerin (Chap. 16) and of synthetic resins of the alkyd type (Chap. 16). It is widely used as a humectant, *i.e.*, a moistening agent, and for this purpose is a constituent of chewing tobacco, stamping inks, and many food products.

Effect of Hydroxyl Groups on Properties. This is brought out by the data of Table 42.

TABLE 42 | **Effect of Hydroxyl Groups on Physical Properties**

NAME	M.P. °C	B.P. °C	SP. GR. 20/4	DIELECTRIC CONSTANT	SOLUBILITY	
					in ether g./100 g	in water g./100 g.
Propane	−190	−44	0.585 [a]	1.8	sol	insol.
1-Propanol	−127	99	0.804	22.4	misc.	misc.
1,2-Propanediol		189	1.038 [b]	40	12	misc.
1,2,3-Propanetriol	18	290	1.260	56.2	insol	misc.

[a] At − 44°. [b] At 23°.

The increase in melting point, boiling point, and dielectric constant is especially marked. This can be explained as a result of association which accompanies the presence of the hydroxyl group. Another effect is on the solubility in ether, for this is reversed from propane to propanetriol (glycerol). The high dielectric constant of glycerol is consistent with the poor solubility of glycerol for nonpolar liquids, and with its good solubility for a number of highly ionized inorganic salts, for example sodium chloride.

Polyhydric alcohols having four or more hydroxyl groups are solids (Table 107, Chap. 42).

HALOHYDRINS

The simplest halohydrins are monohalogenated monohydric alcohols. Those in which the halogen atom and the hydroxyl group are attached to the same carbon atom are unstable, for they spontaneously undergo dehydrohalogenation to form aldehydes or ketones. The common halohydrins are those resulting from the addition of hypohalous acids to olefins. Sometimes they are named this way, for example, ethylene chlorohydrin, CH_2ClCH_2OH. Originally, however, this was called ethylene glycol chlorohydrin, in the same way that glycerol monochlorohydrin was named, as the result of the reaction of hydrochloric acid on the hydroxy compound. Chlorohydrins are the more important of the halohydrins. The I.U.C. system of nomenclature is quite useful.

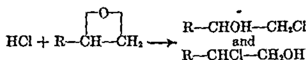
Chlorohydrins are prepared by

1. *Addition of hypochlorous acid to olefins.* This reaction takes place when chlorine gas and ethylene gas are separately passed into water, with vigorous agitation; or hypochlorous acid may be formed by the action of a weak acid (boric, carbonic, etc.) on bleaching powder.



$$HOCl + RCH{=}CH_2 \longrightarrow R{-}CHOH{-}CH_2Cl$$

2. *Reaction of hydrochloric acid with olefin oxides (epoxides)*; with unsymmetrical oxides, mixtures are obtained.



3. *Reaction of hydrochloric acid with glycols, glycerol, etc.* This reaction takes place when hydrogen chloride gas is bubbled into ethylene glycol at 150°.



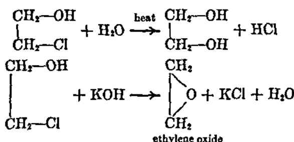
$$HCl + CH_2OH{-}CH_2OH \longrightarrow CH_2Cl{-}CH_2OH + H_2O$$

TABLE 43 | Some Halohydrins

NAME		FORMULA	B.P. °C	SOLUBILITY IN WATER
I.U.C.	halohydrin			
2-Chloroethanol	Ethylene	$ClCH_2CH_2OH$	128.8	misc.
2-Bromoethanol	Ethylene	$BrCH_2CH_2OH$	150	misc.
2-Chloro-1-propanol		$CH_3CHClCH_2OH$	133–134	sol.
3-Chloro-1-propanol	Trimethylene	$ClCH_2CH_2CH_2OH$		
1-Chloro-2-propanol	Propylene	$CH_3CHOHCH_2Cl$	126–127	misc.
2-Bromo-1-propanol		$CH_3CHBrCH_2OH$	52.3*	

* 16 mm.

Chlorohydrins obtained from olefins are of industrial importance as a source of glycols, which result on hydrolysis (see Glycols), and of olefin oxides (epoxyalkanes), which are obtained by heating with strong bases.



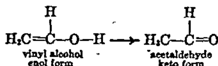
UNSATURATED ALCOHOLS

Unsaturated alcohols are the monohydroxy derivatives of the unsaturated hydrocarbons and possess the properties of unsaturated compounds and of alcohols. However, simple compounds are not known in which the hydroxyl group is joined directly to an unsaturated carbon atom since these are unstable, as mentioned under vinyl alcohol. In order that the compound may be stable, the hydroxyl group must be separated by at least one carbon atom from the unsaturated carbon atom.

Nomenclature of Unsaturated Alcohols. In naming unsaturated alcohols by the I.U.C. system, which is the best, the suffix -en represents the double bond, -yn (or -in) the triple bond, and -ol the hydroxyl group. The longest chain containing the two functional groups is selected, and the carbon atom holding the hydroxyl group is given the smaller number. Sometimes, especially in older literature, the position of the double bond is represented by the Greek letter delta Δ, followed by a superscript indicating the position of the double bond. Thus, $CH_2{=}CHCH{=}CHCH_2OH$ is 2,4-pentadiene-1-ol or $\Delta^{2,4}$-pentadiene-1-ol.

Vinyl Alcohol, Ethenol, $CH_2{=}CHOH$. This would be the simplest unsaturated alcohol. However, vinyl alcohol is not known, although there are many stable compounds which contain the vinyl radical, as for example, vinyl chloride, $CH_2{=}CHCl$, vinyl bromide, $CH_2{=}CHBr$, vinyl acetate, $CH_2{=}CH{-}O{-}CO{-}CH_3$, ethyl vinyl ether, $CH_2{=}CH{-}O{-}CH_2CH_3$, and divinyl ether, $CH_2{=}CH{-}O{-}CH{=}CH_2$.

If attempt is made to prepare vinyl alcohol, as, for example, by hydrolysis of ethyl vinyl ether in dilute sulfuric acid, vinyl alcohol is not obtained. Instead, acetaldehyde or one of its reaction products is formed. Vinyl alcohol, if formed, isomerizes to acetaldehyde.



The hydrogen atom of the hydroxyl group migrates to the second carbon atom, with a change in the nature of the bonds, as indicated. The two com-

pounds are isomeric. The unsaturated alcohol is called the *enol form*, from the I.U.C. name, and acetaldehyde is called the keto form since it contains a carbonyl group, C=O, which is characteristic of ketones. The isomerism differs from other kinds in being dynamic, and is therefore isomerization. It is called **keto-enol isomerization.**

In general, hydroxy compounds are unstable if the hydroxyl radical is attached to an ethylenic carbon atom; such an enol changes spontaneously to the isomeric keto (C=O) compound. However, some enol compounds are known. These are complicated in structure (see Ethyl Acetoacetate and β-Diketones, Chap. 19)

An understanding of the tendency of an enol to change to the corresponding keto form rests upon the energy changes involved. Calculation from bond energies shows that the change of gaseous ethenol to gaseous acetaldehyde is exothermic and that ΔH is -14.7 kcal. In this case ΔH and ΔF are essentially equivalent, for $T\Delta S$ is small owing to the fact that reactant and product are similar as regards number of molecules and molecular complexity (see p. 24). Thus the equilibrium constant at 25° has a value of about 10^{10}, which means that the reverse reaction of acetaldehyde to vinyl alcohol is insignificant. In the liquid state also the equilibrium lies well on the side of the aldehyde.

The reverse reaction of **enolization** (acetaldehyde to vinyl alcohol) is promoted by the addition of alkali, since alcohols are weak acids. Vinyl alcohol is a stronger acid than ethyl alcohol, owing to the presence of the double bond. It will be recalled that the unsaturated hydrocarbon, acetylene, although only weakly acidic, has much more pronounced acidic properties than has ethane. The process of enolization is important in connection with some reactions of aldehydes and ketones.

Allyl Alcohol, 2-Propene-1-ol, $CH_2{=}CHCH_2OH$. Allyl alcohol is the simplest known unsaturated alcohol. The isomeric alcohols, 1-propene-1-ol and 1-propene-2-ol are unstable, for as in vinyl alcohol, the hydroxyl radical is attached to an unsaturated carbon atom. Some allyl compounds occur naturally. Allyl sulfide, $(CH_2{=}CHCH_2)_2S$, is the main constituent of oil of garlic (L. *allium*, garlic). It is present also in onions. Allyl isothiocyanate, $CH_2{=}CHCH_2{-}N{=}C{=}S$, occurs in oil of mustard in combination with glucose.

Allyl alcohol usually is prepared in the laboratory from glycerol by heating glycerol formate or a mixture of glycerol and formic acid. The reactions, complicated in nature, are described under esters of dibasic acids (Chap. 16). Allyl alcohol is produced by the hydrolysis of allyl chloride (p. 117) with hot water.



$$CH_2{=}CHCH_2Cl + H_2O \longrightarrow CH_2{=}CHCH_2OH + HCl$$

Allyl alcohol is a pungent, colorless liquid and a mild lachrymator. Its physical properties are listed in Table 44.

Allyl alcohol undergoes the reactions predictable from its structure, for it exhibits the usual properties of an alcohol and of an unsaturated compound. Its structure is proven by its behavior on reduction and oxidation: *n*-propyl alcohol is obtained by hydrogenation, thus proving that the hydroxyl group is attached to a terminal carbon

atom; mild oxidation with silver oxide yields both an unsaturated aldehyde and acid of three carbon atoms. Permanganate rapidly attacks the double bond, and dichromic acid oxidizes the alcoholic group preferentially.

TABLE 44 | Some Unsaturated Alcohols

NAME		FORMULA	B.P. °C	SP. GR. 20/4	SOLY. IN H_2O
I.U.C.	trivial				
2-Propene-1-ol	Allyl Alcohol	$CH_2{=}CHCH_2OH$	97.0	0.855	misc.
2-Butene-1-ol	Crotyl Alcohol	$CH_3CH{=}CHCH_2OH$	117–8	.853	16
3-Butene-1-ol	Isocrotyl Alcohol	$CH_2{=}CHCH_2CH_2OH$	114	.848	
3-Propyne-1-ol	Propargyl Alcohol	$CH{\equiv}CCH_2OH$	114–5	.972	misc.

The double bond enhances the ease with which the hydroxyl group reacts. With concentrated hydrohalic acids allyl alcohol resembles secondary alcohols in reactivity. Addition of hydrogen halides to the double bond is negligible under these conditions.



$$CH_2{=}CHCH_2OH + HBr \longrightarrow CH_2{=}CHCH_2Br + H_2O$$

Sulfuric acid causes darkening. This is a result of polymerization, promoted by the acid, as in the case of olefins.

PROBLEMS

1. Write formulas and names of stable compounds, as follows:

a) C_4 saturated glycols, normal structure
b) C_4 saturated glycols, having a branched carbon chain
c) C_5 saturated glycols, normal structure
d) C_5 saturated glycols, having a branched carbon chain
e) C_4 saturated chlorohydrins, normal structure
f) C_4 saturated bromohydrins, having a branched carbon chain
g) C_4 unsaturated alcohols, normal structure
h) C_4 unsaturated alcohols, branched carbon chain

2. Indicate the possibility of *cis, trans*-stereoisomerism in the case of the following:

a) 2-butene-1-ol
b) 3-butene-1-ol
c) 2-pentene-1-ol
d) 3-pentene-1-ol
e) 4-pentene-1-ol
f) 3-pentene-2-ol
g) 3-hexene-2-ol
h) 4-hexene-3-ol

3. Write balanced equations, with actual reagents, for a practical laboratory preparation of propylene glycol from:

a) propylene bromide
b) propylene
c) *n*-propyl alcohol
d) isopropyl alcohol
e) *propylene chlorohydrin*
f) allyl alcohol
g) propylene oxide
h) propylene bromohydrin

4. Write balanced equations, with actual reagents, showing how 2,3-butanediol may be obtained from:

a) 2-butene
b) 1,2-dimethylethylene oxide
c) 2-butanol
d) 1-butanol
e) 3-chloro-2-butanol
f) 3-bromo-2-butanol

5. Write the structure of the unsaturated hydrocarbon and the formula of the reagent which would be expected to give the following compound:

a) 1-chloro-2-propanol
b) 1-bromo-2-propanol
c) 3-chloro-2-butanol
d) 3-bromo-2-butanol
e) 1-bromo-2-butanol
f) 1-chloro-2-butanol
g) 1-chloro-2-methyl-2-butanol
h) 1-chloro-2-ethyl-2-butanol

6. Write a balanced equation for the principal reaction of the following reagent with crotyl alcohol:

a) bromine
b) chlorine
c) acetyl chloride
d) phosphorus trichloride
e) dichromic acid
f) methylmagnesium iodide
g) potassium permanganate (neutral)
h) concentrated hydrobromic acid
i) concentrated hydriodic acid (1 mole)
j) concentrated hydriodic acid (2 moles)

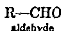
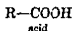
7. Describe a convenient chemical test, stating reagent, conditions, solvent, if any, and readily detectable change, that serves to distinguish between:

a) 1-hexene and allyl alcohol
b) 2-hexyne and crotyl alcohol
c) allyl alcohol and *tert*-butyl alcohol
d) allyl alcohol and ethylene glycol
e) ethylene glycol and ethylene chlorohydrin
f) propylene glycol and propylene bromohydrin
g) ethylene glycol and 1-butanol
h) 2-butanol and 3-chloro-2-butanol
i) 2-chlorobutane and 3-chloro-2-butanol
j) crotyl alcohol and 1,2-butanediol

CHAPTER 12

Monobasic Carboxylic Acids, Fatty Acids

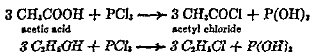
Primary monohydric alcohols are oxidized by aqueous dichromate and sulfuric acid to volatile aldehydes and acids (Chap. 10).

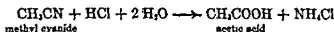
The acids belong to a homologous series called the fatty acid series because many of them occur in combination with glycerol as fats.

The most important member of this series is acetic acid, obtained by the oxidation of ethyl alcohol. It is desirable to mention first some of the general features of the series such as structure, nomenclature, acid properties, etc., and for this purpose acetic acid will be taken as an example.

Structure of Acetic Acid, CH_3COOH. The presence of the hydroxyl group in the molecule of acetic acid is indicated by its behavior with phosphorus trichloride.

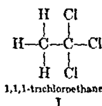


The reaction bears a resemblance to the behavior of ethyl alcohol with phosphorus trichloride in that one oxygen atom and one hydrogen atom are replaced by chlorine. The presence of a methyl group in the acetic acid molecule is indicated by the observation that methyl cyanide, CH_3CN, which can be obtained by the action of potassium cyanide upon methyl iodide and in whose molecule a methyl group is joined to carbon, yields acetic acid and ammonium chloride when heated with hydrochloric acid.

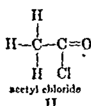


On the basis of **least possible change,** a methyl radical is present in acetic acid and is attached to a carbon atom, as in methyl cyanide. Thus it can be concluded that both a methyl and a hydroxyl radical are attached to a carbon atom in the acetic acid molecule. The position of the second oxygen atom

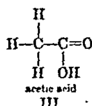
is settled by the observation that when acetyl chloride is heated with phosphorus pentachloride, 1,1,1-trichloroethane, I, is formed.



1,1,1-trichloroethane
I

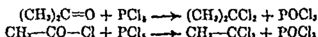


acetyl chloride
II



acetic acid
III

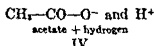
In general, an oxygen atom attached to a carbon atom by a double bond can be replaced by two chlorine atoms on treatment with phosphorus pentachloride. Thus acetone, $(CH_3)_2C{=}O$, and acetyl chloride react similarly.



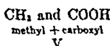
$$(CH_3)_2C{=}O + PCl_5 \longrightarrow (CH_3)_2CCl_2 + POCl_3$$
$$CH_3{-}CO{-}Cl + PCl_5 \longrightarrow CH_3{-}CCl_3 + POCl_3$$

It would appear, therefore, that in acetyl chloride the oxygen atom is attached to the carbon atom by a double bond, as shown in II above. Thus in acetic acid also the oxygen atom is attached by a double bond. These facts are best accounted for by formula III, above.

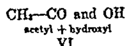
Radicals of Acetic Acid. The molecule of acetic acid may be regarded as being made up of three different pairs of radicals, as shown by IV, V, and VI.



$CH_3{-}CO{-}O^-$ and H^+
acetate + hydrogen
IV



CH_3 and COOH
methyl + carboxyl
V



$CH_3{-}CO$ and OH
acetyl + hydroxyl
VI

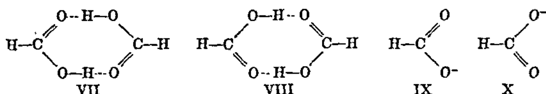
On the basis of IV, *acetic acid is composed of negative acetate* ion and positive hydrogen ion. These are the ions which usually are regarded as being formed when acetic acid is dissolved in water or other solvent of high dielectric constant. Actually in water the positive ion is the hydronium ion, H_3O^+.

On the basis of V, acetic acid is the **carboxyl** derivative of methane. The carboxyl group (CO, *carbonyl* + OH, hydr*oxyl*) is the group which is characteristic of carboxylic acids, such as the fatty acids. Thus, any monocarboxylic acid may be regarded as the monocarboxy derivative of a hydrocarbon.

On the basis of VI, acetic acid is the *acetyl* derivative of water. The acetyl radical, $CH_3{-}CO{-}$ is an example of an *acyl* radical, R—CO—. Acyl radicals bear the same relation to acids that alkyl radicals bear to alcohols. The name of any acyl radical is derived from the name of the acid of which it is a constituent, by changing the suffix -ic to -yl; thus, acetyl, $CH_3{-}CO$, from acetic acid, $CH_3{-}CO{-}OH$; propionyl, $C_2H_5{-}CO$, from propionic acid, $C_2H_5{-}CO{-}OH$, etc. (*Chemical Abstracts* uses the abbreviation Ac to represent the acetyl, not the acetate radical.)

Resonance of Carboxylic Acids and Carboxylate Ions. The heat of combustion of acetic acid, *viz.*, 209.4 kcal. per mole, is lower by 30 kcal. than when calculated from bond energies, taking into account the resonance energy

of carbon dioxide (Tables 7, p. 17, and 9, p. 21). In the case of formic acid the discrepancy amounts to 20 kcal. Formic acid in the vapor state is dimeric. Measurements by means of electron diffraction have shown that the intermolecular oxygen-to-oxygen distance is 2.67 Å. This is interpreted to mean that oxygen atoms of different molecules are attached by hydrogen bonds, for ordinarily oxygen atoms of different molecules do not approach closer than 3 Å. The greater-than-expected stability, the dimeric structure, and the closeness of approach are best explained as the result of resonance between two equivalent forms, VII and VIII.



Acetic acid, which also in the vapor is mainly dimeric, is believed to have a similar structure.

Formate ion, which has a resonance energy of about 36 kcal. (Table 9), is regarded as resonating between structures IX and X. The existence of these two equivalent forms is believed to account for the large resonance energy (refer to Effect of Resonance on Bond Energies, Chap. 2). The negative ions of other carboxylic acids are similar. The slight reactivity of the carbonyl (C═O) bond in acids and salts, as compared to the same bond in aldehydes, ketones, and esters, is believed to be related to stabilization through resonance.

Acetic acid owes its acidic character to the fact that the resonance energy of the negative ion exceeds that of the acid, as in the case of nitric acid (p. 21). Acetic acid is weaker than nitric acid, however. This is because acetate ion is stabilized by resonance only 8 kcal. more than acetic acid, whereas nitrate ion is stabilized 20 kcal. more than nitric acid (Table 9).

Physical Properties of the Series. In Table 45 are listed the physical constants of a number of normal fatty acids. The melting point of an acid containing an odd number of carbon atoms is lower than the next preceding acid, and the melting-point values reach a minimum with valeric acid. The higher values for the acids as compared with the corresponding alcohols result from a higher degree of association in the acids; for example, acetic acid is bimolecular in the vapor state. The downward trend at first appears to result from decreased association resulting from the increase in the size of the alkyl group, and the upward trend after valeric acid from the usual increase associated with increasing molecular weight. The higher values of the even-numbered result from a closer packing of these molecules in the solid state. This [illegible]

The manner in which the boiling points, densities, and solubilities in water change as the molecular weight increases, in general, resembles the behavior of the alcohols.

The liquid acids are, in general, completely miscible with both ether and concentrated sulfuric acid, while the solubility in water decreases progressively.

TABLE 45 | Physical Constants of Normal Saturated Acids, $C_nH_{2n+1}COOH$

NAME	FORMULA	M.P. °C	B.P. °C	SP. GR. 20°/4°	$K_a \times 10^5$	SOLY. IN H_2O G./100 G	SOLY., K SALT IN H_2O G./100 G.	HEAT COMB. KCAL. PER MOLE
Formic	HCOOH	8.40	100.5	1.220	18.1	misc.	76.8	62.8
Acetic	CH_3COOH	16.60	118.1	1.049	1.76	misc.	255^{20}	209.4
Propionic	C_2H_5COOH	−22.0	141.1	0.992	1.34	misc.	178^{16}	365
Butyric	C_3H_7COOH	−5.55	163.5	0.959	1.50	misc.	297^{31}	520
Valeric	C_4H_9COOH	−34.5 [a]	187.0	0.942	1.38	3.7	sol.	679
Caproic	$C_5H_{11}COOH$	−3.2	205.3	0.929	1.32	0.97	sol.	831
Enanthic	$C_6H_{13}COOH$	−6.2	222.5	0.922	1.4	.24	.	986
Caprylic	$C_7H_{15}COOH$	16.3	239.3	0.910	1.4	.068		
Pelargonic	$C_8H_{17}COOH$	12.2	254.4	0.907	1.1	.026		1287
Capric	$C_9H_{19}COOH$	31.2	268.7	0.895 [b]		.015		1453
Lauric	$C_{11}H_{23}COOH$	43.9	225.0 [a]	0.883 [b]		.0055		1772
Myristic	$C_{13}H_{27}COOH$	54.1	250.5 [a]	0.858 [b]		.0020		2086
Palmitic •	$C_{15}H_{31}COOH$	62.7	269 [a]	0.853 [b]		.0007		2380
Stearic	$C_{17}H_{35}COOH$	69.6	287 [a]	0.847 [b]		.0003		2698

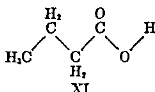
[a] At 100 mm. [b] At m.p.

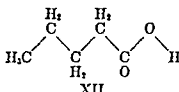
The solubilities in water of the sodium and potassium salts when expressed in grams actually increase for the first few members, but in general when expressed as molal solubilities suffer a small decrease. The potassium salts are usually much more soluble than the sodium salts. With increase in molecular weight the solubilities of these salts gradually decrease, but in the case of the acids heavier than butyric it is evident that the salts are much more soluble in water than the acids themselves. In the nonpolar solvents like the hydrocarbons these salts are practically insoluble while in the alcohols they are moderately soluble. Salts of other metals are in general less soluble than the sodium and potassium salts, and when they are insoluble, they can be obtained by the addition of the metal ions to solutions of the sodium or potassium salts (see Soaps, p. 246).

The ionization of formic acid is much greater than that of acetic, but not much difference is to be noted in the other acids. The introduction of the first alkyl radical in replacing the hydrogen atom of formic acid by a methyl group produces more of an effect than increasing the size of the alkyl radical by further substitution.

The zigzag nature of the carbon chain in the higher fatty acids has been demonstrated in the case of their monomolecular films on water. Measurement of the thickness of these films has shown that the molecules are standing on end with the carboxyl group in the water phase and the hydrocarbon part of the molecule projecting upwards as a zigzag chain. Moreover, crystal structure measurements on the solid acids have shown that here also the carbon atoms are arranged in zigzag fashion. In a molecule

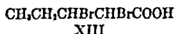
of butyric acid the methyl and carboxyl groups lie on opposite sides of the chain, XI, while in valeric acid they lie on the same side, XII.

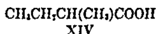




The arrangement of the atoms in butyric acid is characteristic of acids having an even number of carbon atoms, and in valeric acid of those having an odd number of carbon atoms. The manner in which molecules of solid acids are oriented in the solid state is different for the two groups of acids and this accounts for the higher melting points of the even-numbered acids.

Nomenclature. The monocarboxylic acids usually are known by the common names, as listed in Table 45. Generally these names are used in *Chemical Abstracts.* In the I.U.C. system the acids are named from the hydrocarbon of the same number of carbon atoms by changing the ending -e to -oic. Thus C_2H_5COOH is propanoic acid. Substituted acids are named differently: in the I.U.C. system the carboxyl group occupies position 1, the adjacent carbon atom is 2, the next is 3, and so on; in the other system, preferred by the American Chemical Society, the carbon atoms are indicated by the Greek letters *alpha, beta, gamma*, etc. (α, β, γ), starting *next* to the carboxyl group. Thus XIII is either 2,3-dibromopentanoic acid or α,β-dibromovaleric acid. An unsubstituted acid having a branched carbon chain often is named as a substituted acetic acid; for example, XIV is either α-methylbutyric acid or methylethylacetic acid.





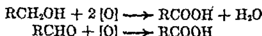
General Methods of Preparation. Of these, air oxidation of aldehydes is important commercially for acetic acid; convenient laboratory methods are oxidation of primary alcohols, hydrolysis of alkyl cyanides, and carbonation of Grignard reagents. Acids are formed when many types of organic compounds are oxidized, for example, olefins with alkaline permanganate and olefins with ozone. Also, partial oxidation of alkanes with air at high temperatures yields acids, usually mixtures. Special methods employed in the manufacture of formic and acetic acids are mentioned under these acids.

1. *Gas phase oxidation of aldehydes.* When air and the vapor of an aldehyde under pressure are passed over a suitable heated catalyst, oxidation takes place smoothly. Vanadium or cerium oxide is an especially good catalyst, giving essentially quantitative yields of acetic acid from acetaldehyde. Many other metallic compounds can be used, for example, manganese acetate.



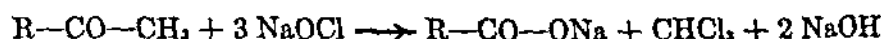
From bond and resonance energies, ΔH is about -65 kcal. Because of the strongly exothermic nature of the reaction, control is necessary. This is fundamentally an important point, since oxidation of aldehydes by means of oxidizing agents would be expected to be strongly exothermic also.

2. *Oxidation of primary alcohols and of aldehydes.* In aqueous solution the oxidation of alcohols is the more important reaction, since they are more readily available than aldehydes. Dichromic acid is much used (p. 147). Alkaline permanganate smoothly oxidizes alcohols to acids without the complication of aldehyde formation, as when dichromate is used. Alkaline hydrogen peroxide is especially useful with aldehydes.



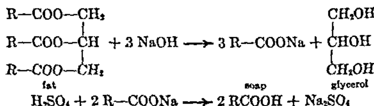
$$RCH_2OH + 2\,[O] \longrightarrow RCOOH + H_2O$$
$$RCHO + [O] \longrightarrow RCOOH$$

3. *Oxidation of methyl ketones.* Normal ketones are cleaved on oxidation with alkaline permanganate to two acids (p. 276). Methyl ketones undergo the haloform reaction to yield a haloform and an acid (p. 262).



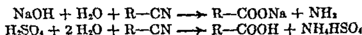
$$R{-}CO{-}CH_3 + 3\,NaOCl \longrightarrow R{-}CO{-}ONa + CHCl_3 + 2\,NaOH$$

4. *Hydrolysis of esters* (especially fats). Esters (Chaps. 15 and 16) undergo hydrolysis best under alkaline conditions (saponification). Fats are esters of glycerol with higher fatty acids (glycerides), and are the chief source of many of these acids. Saponification of fats yields glycerol and the sodium salts of the acids (soaps) from which the acids are liberated on the addition of a strong acid.



$$H_2SO_4 + 2\,R{-}COONa \longrightarrow 2\,RCOOH + Na_2SO_4$$

5. *Hydrolysis of alkyl cyanides* (nitriles), by heating with a strong base or a strong acid, in the presence of water.



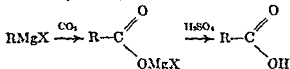
$$NaOH + H_2O + R{-}CN \longrightarrow R{-}COONa + NH_3$$
$$H_2SO_4 + 2\,H_2O + R{-}CN \longrightarrow R{-}COOH + NH_4HSO_4$$

By means of the nitrile synthesis (p. 110) and hydrolysis of the resulting nitrile, an acid may be obtained from the next lower alcohol through the bromide or iodide.



$$R{-}OH \longrightarrow R{-}Br \longrightarrow R{-}CN \longrightarrow R{-}COOH$$

6. *Carbonation of Grignard reagents.* This is best accomplished by adding the solution of the Grignard reagent to solid carbon dioxide (p. 128). The addition product is decomposed by the addition of dilute sulfuric acid.



$$RMgX \xrightarrow{CO_2} R{-}C(=O){-}OMgX \xrightarrow{H_2SO_4} R{-}C(=O){-}OH$$

As in the nitrile synthesis, an acid usually can be prepared from the next lower alcohol.

7. *Synthesis with malonic ester or acetoacetic ester.* These methods, described in Chapter 19, are useful in the synthesis of higher acids.

8. *Miscellaneous methods.* Oxidation of alkenes, especially by alkaline permanganate, yields salts of acids by cleavage at the double bond. Partial gas phase oxidation of alkanes at high temperature gives complex mixtures of aldehydes and acids. The Synthol modification (p. 153) of the Fischer-Tropsch reaction of carbon monoxide and hydrogen, carried out at about 600° F. and 25 atmospheres pressure over an iron catalyst gives acids, along with other products. This method promises to develop into the most economical industrial source of aliphatic acids.

General Reactions of Acids. The characteristic reactions of acids are those which are due to the presence of the carboxyl radical, the functional group of acids. These reactions are described first. Typical reactions of the alkyl radical, for example, oxidation and substitution, are described last. Acetic acid is taken as a typical acid. It should be noted that although homologs of acetic acid undergo the same reactions, usually they react at lower rates.

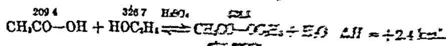
1. *Ionization to give hydronium ions in water, or other onium ions in some other ionizing solvent.*



$$H_2O + CH_3COOH \rightleftharpoons CH_3COO^- + H_3O^+$$

Carboxylic acids are weak, in comparison with strong acids such as nitric and sulfuric acids, but sufficiently strong to show the characteristic behavior of acids, for example, formation of salts with bases and with salts of weaker acids, and liberation of hydrogen with active metals. These reactions, with the exception of the last, are very rapid, for they are typical ionic reactions.

2. *Ester formation with alcohols.* These reactions are very slow; however, they are markedly increased by catalysis. Strong proton donors are the best catalysts, for example, hydrogen chloride and hydrogen sulfate. Ethyl acetate is formed when acetic acid reacts with ethyl alcohol.



$$\underset{209\ 4}{CH_3CO{-}OH} + \underset{326\ 7}{HOC_2H_5} \overset{H_2SO_4}{\rightleftharpoons} \underset{\text{ethyl acetate}}{CH_3CO{-}OC_2H_5} + H_2O \quad \Delta H = +2.4\ \text{kcal}$$

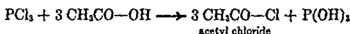
Other acids and/or other alcohols may react. The reaction, usually spoken of as **esterification**, is reversible (see Esterification, p. [illegible]).

Methyl esters result from a special type of reaction, that of acids with diazomethane, CH_2N_2.



$$CH_3COOH + CH_2N_2 \longrightarrow CH_3COOCH_3 + N_2$$

3. *Acid chloride formation.* Many inorganic acid chlorides [illegible] ganic acids to form the acid chloride of the organic acid. [illegible] phosphorus trichloride, phosphorus pentachloride, and [illegible] typical.



$$PCl_3 + 3\,CH_3CO{-}OH \longrightarrow 3\,\underset{\text{acetyl chloride}}{CH_3CO{-}Cl} + P(OH)_3$$

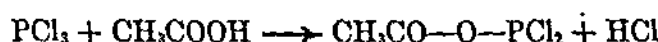


$$PCl_5 + CH_3CO{-}OH \longrightarrow CH_3CO{-}Cl + POCl_3$$

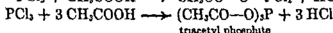


$$SOCl_2 + CH_3CO{-}OH \longrightarrow CH_3CO{-}Cl + SO_2 + HCl$$

The reactions usually are fairly rapid. Phosphorus pentachloride reacts exothermically. Side reactions take place in the case of phosphorus trichloride, leading to the formation of hydrogen chloride and of compounds of anhydride character.



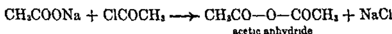
$$PCl_3 + CH_3COOH \longrightarrow CH_3CO{-}O{-}PCl_2 + HCl$$



$$PCl_3 + 3\,CH_3COOH \longrightarrow \underset{\text{triacetyl phosphite}}{(CH_3CO{-}O)_3P} + 3\,HCl$$

A modification of the reaction is the use of the sodium salt of the acid (see p. 213).

4. *Anhydride formation.* This takes place when the sodium salt of the acid is heated with the acid chloride (see Chap. 15).



$$CH_3COONa + ClCOCH_3 \longrightarrow \underset{\text{acetic anhydride}}{CH_3CO{-}O{-}COCH_3} + NaCl$$

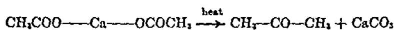
5. *Amide formation.* When the ammonium salt of an acid is heated to about 150° (under pressure), the amide is formed slowly by elimination of water.



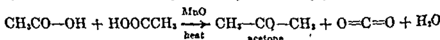
$$CH_3COOH + NH_3 \longrightarrow \underset{\text{acetamide}}{CH_3CONH_2} + H_2O$$

The heat effect is small (ΔH from bond energies and resonance energies is +1.9 kcal.), and the reaction is reversible. At 212° the acid is 84 per cent converted at equilibrium, and in 1 hour the reaction has proceeded 98 per cent of the way toward equilibrium. The reaction appears to be acid catalyzed, for it proceeds conveniently when ammonium acetate is heated in glacial acetic acid.

6. *Decarboxylation.* Acids may lose carbon dioxide in two ways, one molecule from one molecule of the acid to form a hydrocarbon, or one molecule from two molecules of the acid to form a ketone. The first reaction takes place when a suitable salt of the acid is heated with a strong base (sodium hydroxide, soda lime), the second when a suitable salt is heated alone, or the acid is passed over a hot, suitable catalyst.



$$CH_3COO{-}Ca{-}OCOCH_3 \xrightarrow{\text{heat}} CH_3{-}CO{-}CH_3 + CaCO_3$$

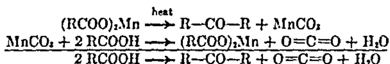


$$CH_3CO{-}OH + HOOCCH_3 \xrightarrow[\text{heat}]{MnO} \underset{\text{acetone}}{CH_3{-}CO{-}CH_3} + O{=}C{=}O + H_2O$$

When sodium salts of higher acids, RCOONa, are heated with sodium hydroxide, side reactions take place with the formation of other products, mainly hydrocarbons, saturated and unsaturated, of molecular weight close to that of R.

Many salts of bivalent and higher valence metals yield ketones when heated. The oxides or carbonates of many of these can catalyze the decomposition of

the acids at temperatures of 400° or higher. Especially effective is manganese oxide, manganese carbonate, thorium oxide, or barium carbonate. A cycle of reactions is involved as shown in the case of manganese carbonate, with the result that a small amount of carbonate can promote the decomposition of a large amount of acid.



$$(RCOO)_2Mn \xrightarrow{heat} R{-}CO{-}R + MnCO_3$$
$$MnCO_3 + 2\ RCOOH \longrightarrow (RCOO)_2Mn + O{=}C{=}O + H_2O$$
$$2\ RCOOH \longrightarrow R{-}CO{-}R + O{=}C{=}O + H_2O$$

The overall gas phase decarboxylation to a ketone would be endothermic ($\Delta H = +11$ kcal.), from bond and resonance energies, if it could take place at ordinary temperature.

7. *Reduction.* The carbonyl group of carboxylic acids and of carboxylate ions, unlike the carbonyl group of aldehydes and ketones, is not easily reduced. Metallic sodium has no reducing action. However, derivatives of acids (esters, anhydrides, and acid chlorides) can be reduced by metallic sodium, or other means (p. 218).

Recently (1947) it has been found that acids can be reduced to primary alcohols *by complex metallic hydrides, for they are powerful reducing agents.* One of the most important of these is lithium aluminum hydride, $LiAlH_4$ (p. 133).

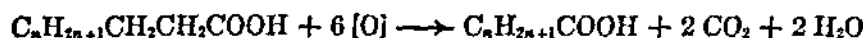


$$4\ R{-}COOH + 3\ LiAlH_4 \longrightarrow (RCH_2O)_3Al + RCH_2OLi + 2\ LiAlO_2 + 4\ H_2$$

An alcohol is obtained from the lithium-aluminum salt by the addition of water or, better, dilute acid. Lithium aluminum hydride also reduces esters, etc., to alcohols.

8. *Oxidation.* Acids, with the exception of formic acid, are reasonably resistant to oxidation by dichromic acid or by permanganate in dilute aqueous solution. For this reason acids are the main oxidation products of aldehydes and primary alcohols. Acetic acid is not changed when heated with chromic anhydride, and for that reason it often is used as a solvent in which to carry out oxidations of other compounds with this reagent. Fatty acids can be oxidized by mixtures of chromic anhydride, sulfuric acid, and water, if the proportion of water is not large. Similarly reacting mixtures may be made from dichromate, in place of chromic anhydride. These are such powerful oxidizing agents that they are able to initiate oxidation at a new place in the molecule, presumably by hydroxylation of $>CH_2$ to $>CHOH$. Once started, the oxidation continues further, finally giving carbonic acid and other degradation products, mainly lower fatty acids, by rupture of the carbon chain.

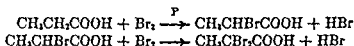
An oxidation of fatty acids that proceeds under control is that with hydrogen peroxide in the presence of an iron salt, which acts catalytically. In this reaction the product is an acid containing two less carbon atoms.



$$C_nH_{2n+1}CH_2CH_2COOH + 6\ [O] \longrightarrow C_nH_{2n+1}COOH + 2\ CO_2 + 2\ H_2O$$

It is believed that oxidation is initiated at the *beta*-carbon atom. This oxidation resembles in some respects the biochemical oxidation of fatty acids in the animal body, for here also the fatty acid is degraded, two carbon atoms at a time. Thus the acids having an even number of carbon atoms finally yield acetic acid, which is oxidized in the body. Acids of naturally occurring fats have an even number of carbon atoms.

9. *Substitution.* Acids, like alkanes, undergo halogenation with chlorine or bromine, though usually somewhat less readily. The reaction is catalyzed by the presence of phosphorus, or of a phosphorus halide. Heating is necessary. Under these conditions substitution takes place at the *alpha*-position. Propionic acid, for example, is converted to α-bromopropionic and α,α,-dibromopropionic acid with bromine.



More recently, acids have been shown to undergo chlorination with sulfuryl chloride when an organic peroxide is added, for example, benzoyl peroxide, $(C_6H_5CO)_2O_2$. Acids above acetic acid react readily, acetic acid slowly. All positions are substituted. For example, *n*-butyric acid yields a mixture of α,β, and γ-chlorobutyric acids, the first in smallest amount.



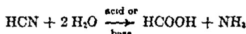
INDIVIDUAL ACIDS

Formic acid and acetic acid are the most important members of the series and will be described in some detail, especially as regards those properties which are different from the general ones.

Formic Acid, Methanoic Acid, HCOOH. Formic acid (L. *formica*, ant) occurs in the free state in the red ant, from which it may be isolated by crushing and steam distilling. It occurs widely in plants, for example, the stinging nettle and pine needles. It has been detected in muscle and blood. In concentrated form it has a pungent odor and produces blisters when placed on the skin.

Formic acid has germicidal properties and on this account is preferred to acetic acid for many industrial purposes as, for example, the deliming of hides and the coagulation of rubber latex. The acid is used extensively in the dye industry.

It is obtained by heating hydrogen cyanide with aqueous acids or bases.



This shows that hydrogen cyanide is the nitrile of formic acid. Also, formic acid is formed when chloroform is heated with alcoholic potassium hydroxide, or when ethyl alcohol or acetaldehyde undergoes the haloform reaction (p. 262).



Sodium formate is manufactured from carbon monoxide and sodium hydroxide by heating at 200° under a pressure of 8 to 10 atmospheres, or higher.

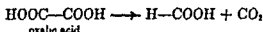


This reaction would appear to indicate that carbon monoxide is the anhydride of formic acid, much as carbon dioxide, which is converted to carbonates with bases, is the anhydride of carbonic acid.



$$CO_2 + 2\,NaOH \longrightarrow Na_2CO_3 + H_2O$$

Formic acid is prepared conveniently in the laboratory by heating oxalic acid in glycerol. The reaction is essentially a decomposition of oxalic acid but proceeds through the intermediate of an ester, glycerol oxalate (see Esters of Dibasic Acids, p. 251).



$$\underset{\text{oxalic acid}}{HOOC{-}COOH} \longrightarrow H{-}COOH + CO_2$$

A dilute formic acid, such as the one obtained above from oxalic acid, may be concentrated by distillation until the constant boiling mixture is obtained which distils at 107° and contains 77 per cent of formic acid. Anhydrous formic acid may be obtained from this by dehydration with boric anhydride. It may be obtained also from the dry lead salt by means of hydrogen sulfide or from the dry sodium salt by treatment with the proper amount of concentrated sulfuric acid.

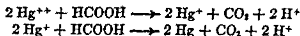
Formic acid has properties which distinguish it from the other acids in that it is easily oxidized to carbonic acid, and can be decomposed in two ways, one to give water and carbon monoxide and the other to give hydrogen and carbon dioxide. These unique reactions, which distinguish it from its homologs, may be ascribed to the presence of the hydrogen atom, instead of an alkyl radical, on the carboxyl carbon atom. The molecule of formic acid contains the grouping of atoms characteristic of aldehydes, *viz.*, H—C=O (see Chap. 17).

1. *Oxidation.* Formic acid is a good reducing agent. Not only is it oxidized by strong oxidizing agents like dichromic acid and permanganate but also by milder ones like mercury and silver salts. When an aqueous solution of mercuric chloride containing formic acid is heated, mercurous chloride is precipitated.



$$2\,HgCl_2 + HCOOH \longrightarrow 2\,HgCl + 2\,HCl + CO_2$$

Similarly, mercuric ion when heated with formic acid is reduced first to mercurous ion and then to metallic mercury.



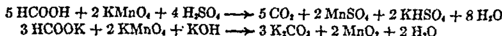
$$2\,Hg^{++} + HCOOH \longrightarrow 2\,Hg^{+} + CO_2 + 2\,H^{+}$$
$$2\,Hg^{+} + HCOOH \longrightarrow 2\,Hg + CO_2 + 2\,H^{+}$$

Silver ion is also reduced.



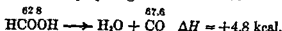
$$2\,Ag^{+} + HCOOH \longrightarrow 2\,Ag + CO_2 + 2\,H^{+}$$

Formic acid is easily oxidized to carbonic acid by acid permanganate and more slowly by boiling with alkaline permanganate solution (distinction from oxalic acid).



$$5\,HCOOH + 2\,KMnO_4 + 4\,H_2SO_4 \longrightarrow 5\,CO_2 + 2\,MnSO_4 + 2\,KHSO_4 + 8\,H_2O$$
$$3\,HCOOK + 2\,KMnO_4 + KOH \longrightarrow 3\,K_2CO_3 + 2\,MnO_2 + 2\,H_2O$$

2. *Decomposition to carbon monoxide and water.* When formic acid or any one of its salts is heated with concentrated sulfuric acid, carbon monoxide is evolved. This is the most convenient method of preparing carbon monoxide.



$$\overset{62.8}{HCOOH} \longrightarrow H_2O + \overset{67.6}{CO} \quad \Delta H = +4.8\ \text{kcal.}$$

The reaction, if it could take place spontaneously in the absence of sulfuric acid would be endothermic, for ΔH is +4 8 kcal., calculated from heats of combustion. However, ΔF is − 4.9 kcal. Thus if reaction could take place at 25°, formic acid would decompose to carbon monoxide and water, for at 25° about 80 per cent would be decomposed at equilibrium (under pressure, to prevent escape of carbon monoxide). However, ordinary formic acid (77%) appears to be quite stable and suffers little or no decomposition, because the rate is essentially zero. But pure anhydrous formic acid slowly decomposes, even at a low temperature.

The effect of a temperature rise on the position of equilibrium is in the direction which would be predicted from the fact that ΔH is positive. At higher temperatures equilibrium is attained in the presence of hydrochloric acid. At 156° the equilibrium constant has a value of 85, and at 218° a value of 264. It is from these and other data that ΔF for the reaction at 25° has been evaluated.

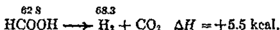
Carbon monoxide is essentially an anhydride of formic acid, but it differs structurally from the anhydrides of other carboxylic acids (Chap. 15). The formation of sodium formate from carbon monoxide and hot moist sodium hydroxide under pressure is essentially the reverse of the decomposition reaction.

3. *Decomposition to yield hydrogen.* Formic acid or, better, formates decompose in contact with some heavy metals, for example, platinum and rhodium. Thus, when rhodium black is added to a solution of sodium formate at 60°, hydrogen and carbon dioxide are evolved.



$$2\,HCOONa + H_2O \longrightarrow Na_2CO_3 + CO_2 + H_2$$

For the decomposition of formic acid alone at 25°, ΔH from heats of combustion is +5.5 kcal.,



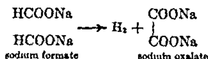
$$\overset{62.8}{HCOOH} \longrightarrow H_2 + \overset{68.3}{CO_2} \quad \Delta H = +5.5 \text{ kcal.}$$

and ΔF is −9.1 kcal. Thus from the equation

$$\Delta H = \Delta F + T\Delta S$$

it can be seen that the value of $T\Delta S$, the entropy change term, is +14.6 kcal., an unusually high value. This is due to the fact that the number of moles of products exceeds the number of moles of reactants, and also that the products are gases, whereas reactants are liquids. Under either of these conditions $T\Delta S$ has a positive value, indicating that there is an increase in entropy. In this particular case the increase in entropy is large for such a simple chemical reaction. It is larger than in the decomposition of formic acid to water and carbon dioxide, for in this case only one of the products is a gas.

Hydrogen is eliminated in another type of reaction, *viz.*, rapid heating of sodium formate to 440° or, better, heating to 360° in the presence of sodium hydroxide.



$$\begin{matrix} HCOONa \\ HCOONa \\ \text{sodium formate} \end{matrix} \longrightarrow H_2 + \begin{matrix} COONa \\ | \\ COONa \\ \text{sodium oxalate} \end{matrix}$$

This reaction is useful for the preparation of sodium oxalate, and thus of oxalic acid.

Acetic Acid, Ethanoic Acid, CH_3COOH. Acetic acid (L. *acetum*, vinegar) is the most common of the organic acids. In dilute aqueous solution it has been known since ancient times, for such solutions result when beverages of low alcoholic content, for example, wine or cider, are exposed to air. Acetic acid occurs widely in plants

sometimes in the free form, sometimes as an ester. The change of alcohol to acetic acid is brought about by the minute fungus, *Mycoderma aceti*, the so-called "mother of vinegar," spores of which are present in the air. This organism elaborates an enzyme, **alcoholoxidase**, which catalyzes the oxidation of alcohol by the oxygen of the air (see p. 147).

Acetic acid is manufactured from acetylene. The first step is the hydration of acetylene to acetaldehyde (p. 84), the second is the oxidation of acetaldehyde catalytically over vanadium oxide, cerium oxide, or other suitable oxide (p. 173). Acetic acid formerly was obtained largely by the process of wood distillation. This source is much less important nowadays.

Acetic acid is concentrated by removing water through distillation, and is purified by cooling, thus allowing acetic acid to freeze. The unfrozen portion, which contains impurities, is removed, usually by centrifugation. Acetic acid so purified is **glacial acetic acid.** Usually its purity is 99.5 per cent or higher.

Cider containing up to 15 per cent alcohol is the usual source of alcohol for vinegar manufacture. In the older Orleans process the alcoholic liquid, often wine, was inoculated with the fungus and the whole was allowed to stand for a long time in a warm place. In the "quick vinegar process" the liquid is allowed to flow slowly over beech-wood shavings while air is forced upwards. In this way all parts of the liquid come in contact with oxygen, due to the greater surface. The operation may be shortened to 8 or 12 days. The optimum temperature is about 35°. Vinegar contains 3 to 6 per cent acetic acid.

In the wood distillation process (see Methanol, p. 150) acetic acid is recovered from crude pyroligneous acid by distillation or by extraction with a suitable solvent. In case lime is used for neutralizing the acid, the dry, crude "gray acetate of lime" is decomposed with concentrated sulfuric acid and the acetic acid is distilled out. By distillation and freezing, glacial acetic acid is obtained.

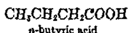
Acetic acid melts at 16.60° and boils at 118.2°. The density, 20°/4°, of the pure acid, 1.0492, increases to a maximum of 1.0748 on the addition of water and then drops to that of water. The composition at the maximum is 78 per cent. The melting point is lowered 2.16° for each 1 per cent of water present. The acid is an excellent solvent and mixes in all proportions with water, alcohol, ether, and most organic liquids. When the concentrated acid is left for a time on the skin, blisters are formed.

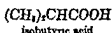
Salts of Acetic Acid. Acetic acid is monobasic and forms, with all bases, salts which for the most part are soluble in water. Some basic acetates such as the basic ferric acetate are insoluble in water. Use is made of this salt in chemical analysis to separate iron from other metals. The sodium salt crystallizes from water in the hydrated form $CH_3CO_2Na \cdot 3\,H_2O$, which melts at 58 to 59°, due to solution of a part of the salt in the water of hydration. At 79 to 80°, it is completely dissolved, and at 120 to 123° the water boils out, leaving a fluffy solid, which at a still higher temperature melts with decomposition to a dark liquid. Other salts of the acid are: the potassium salt, CH_3CO_2K; the calcium salt, $(CH_3CO_2)_2Ca$; the lead salt, or **sugar of lead,** $(CH_3CO_2)_2Pb \cdot 3\,H_2O$; **verdigris,** a basic acetate of copper, $(CH_3CO_2)_2Cu \cdot Cu(OH)_2$; **Paris green,** a mixed acetate and arsenite of copper, $(CH_3CO_2)_2Cu \cdot Cu(AsO_2)_2$; etc. Acetates of iron and aluminum are used in dyeing. When heated with water they form insoluble basic salts which act as mordants by forming insoluble "lakes" with dyes. The fabric is impregnated with the salt, then steamed, and finally put into the dye bath. Dyes so fixed oftentimes are very fast.

Acetic acid is employed extensively in chemical laboratories as a reagent and solvent and in industry for the manufacture of its salts and especially for the synthesis of many organic materials. Among these are acetone, esters, perfumes, dyes, pharmaceuticals, and the plastics, cellulose acetate and polyvinyl acetate. Also it is used in the textile and paper industry, and in the manufacture of "white lead," — a basic carbonate of lead obtained by passing air containing carbon dioxide and the vapor of acetic acid over sheet lead.

Propionic Acid, Propanoic Acid, CH_3CH_2COOH. This acid is present, in small amount, in pyroligeneous acid and is reported to occur in the fruit of *Ginkgo biloba.* It is the first of the fatty acids which can be salted out of an aqueous solution, in the form of a lighter liquid phase, by the addition of calcium chloride. The name denotes this property (Gr. *prōtos*, first + *piōn*, fat).

Butyric Acids, C_3H_7COOH. There are two isomeric fatty acids of four carbon atoms, *viz.*, normal butyric acid and isobutyric acid.


$CH_3CH_2CH_2COOH$
n-butyric acid


$(CH_3)_2CHCOOH$
isobutyric acid

The normal acid is found in butter (L. *butyrum*, butter) in combination with glycerol as a glyceride. It is the simplest acid found in fats. It occurs free in perspiration and in feces. Isobutyric acid occurs free in locust bean and carob bean. Both acids possess disagreeable odors.

Butyric acid is formed when butter becomes rancid, owing to the formation of the uncombined acid from the glyceride, either by hydrolysis or by oxidation. In the latter case, oxidation of the glycerol frees the acid from combination. The disagreeable odor of rancid butter is due to the presence of the uncombined acid. Sugar and starch are converted to butyric acid by a special fermentation induced by *Bacillus butylicus*. Calcium carbonate is added to combine with the acid as it is formed.

Higher Fatty Acids. Acids up to and including myristic acid, $C_{14}H_{28}O_2$, are known to occur naturally. Above this many, up to the C_{30} acid, also occur in nature. Only acids having an even number of carbon atoms are present in fats. Except for a few relatively rare acids, they have a normal carbon chain. The highest saturated acid present in fats to any important extent is stearic acid (see Table 55, p. 248). The acids are in combination with glycerol as glycerides (see Fats, Chap. 16). The most abundant of the saturated acids are the C_{16} and C_{18} acids, namely, palmitic and stearic acids.

The physical properties of the fatty acids are described on pages 171 and 172. The odor varies markedly. Formic and acetic acids possess pungent but not disagreeable odors, and propionic acid has a somewhat similar odor. The odors of butyric and valeric acids are highly disagreeable. Those of caproic, caprylic, and capric acids (L. *caper*, goat) are progressively less disagreeable.

Salts of Higher Fatty Acids. These usually are called soaps. Potassium soaps are soluble in water; even those of palmitic and stearic acids are water soluble. Sodium soaps are less soluble; sodium stearate, for example, is only very slightly soluble, and is essentially insoluble in salt solution. Salts of alkaline earth and heavier metals usually are slightly soluble or insoluble in water. Soaps are described in more detail in connection with fats (Chap. 16).

Detection of Fatty Acids. Acids dissolve in water and the aqueous solutions have an acid reaction, but high molecular weight acids are insoluble.

Acids as complex as C_{18} acids dissolve in aqueous solutions of strong bases, especially potassium hydroxide, to form salts. They also dissolve in concentrated sulfuric acid. Fractional distillation of mixtures of acids is somewhat tedious, due to the pronounced tendency to associate, and thus to form molecular complexes with one another.

The fatty acids differ in the ease with which they distil with steam. The Duclcux number is a measure of this difference. The lower acids up to C_7 distil readily, C_8 to C_{12} acids distil slowly, higher acids are essentially nonvolatile.

Individual acids often are identified by conversion to solid compounds, for example, the amides, $RCONH_2$, or substituted amides, $RCONHR'$. Here R usually is an aromatic radical. When it is phenyl, C_6H_5, the product is an anilide, $RCONHC_6H_5$. An amide is slowly formed by heating the ammonium salt of an acid, an anilide by heating the acid with aniline, $C_6H_5NH_2$.



$$RCOOH + HNHC_6H_5 \longrightarrow RCONHC_6H_5 + H_2O$$

Reaction takes place more rapidly when the acid chloride, RCOCl, reacts respectively with ammonia (or ammonium carbonate) or aniline.

PROBLEMS

1. Name the three sets of radicals present in the molecule of:

a) propionic acid
b) *n*-butyric acid
c) *n*-valeric acid
d) isobutyric acid
e) isovaleric acid
f) trimethylacetic acid

2. Assign to the following two unique names, one of which is based on acetic acid:

a) $(CH_3)_2CHCOOH$
b) $(CH_3)_2CHCH_2COOH$
c) $(CH_3)_2CH(CH_2)_2COOH$
d) $(CH_3)_2CH(CH_2)_3COOH$
e) $(C_2H_5)_2CHCOOH$
f) $(C_6H_5CH_2)_2CHCOOH$
g) $[(CH_3)_2CH]_2CHCOOH$
h) $CH_3CH_2CH(CH_3)COOH$
i) $(CH_3)_3CCOOH$
j) $(CH_3)_3CCH_2COOH$
k) $CH_3CH_2C(CH_3)_2COOH$
l) $CH_3CH_2CH(CH_3)CH_2COOH$
m) $CH_3CH_2C(CH_3)_2CH_2COOH$
n) $(C_6H_5)_3CCOOH$

3. Indicate the steps (arrow and reagents are sufficient) for a practical laboratory preparation of propionic acid from:

a) propionaldehyde
b) *n*-propyl alcohol
c) *n*-propyl chloride
d) ethyl iodide (2 methods)
e) ethyl alcohol (2 methods)
f) ethyl propionate

4. Write balanced equations with the actual reagents for a practical laboratory preparation of isobutyric acid:

a) from a salt
b) by oxidation of an aldehyde with dichromate
c) by oxidation of an alcohol with dichromate
d) by oxidation of an aldehyde with alkaline permanganate
e) by oxidation of an alcohol with alkaline permanganate
f) by oxidation of an olefin with alkaline permanganate
g) by the nitrile synthesis, from an alcohol

h) by the Grignard synthesis, from an alcohol
i) by the hydrolysis of an ester
j) by the saponification of a glyceride

5. Indicate the steps (arrows and reagents) for a practical laboratory preparation of the following from propionic acid:

a) lithium propionate
b) calcium propionate
c) potassium propionate
d) methyl propionate
e) ethyl propionate
f) isopropyl propionate
g) propionyl chloride
h) propionyl bromide
i) 1,1,1-trichloropropane
j) propionic anhydride
k) propionamide
l) ethane
m) α-bromopropionic acid
n) α-chloropropionic acid
o) diethyl ketone
p) propane

6. Indicate the steps (arrows and reagents) for a practical laboratory preparation of the following from *n*-propyl alcohol:

a) *n*-butyric acid
b) isobutyric acid
c) propionyl chloride
d) *n*-valeric acid
e) isovaleric acid
f) α-bromo-*n*-butyric acid

7. Describe a reasonably rapid chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) *n*-propyl alcohol and propionic acid
b) formic acid and acetic acid
c) *n*-octane and acetic acid
d) sodium acetate and sodium formate
e) sodium acetate and sodium ethoxide
f) formic acid and methanol
g) sodium acetate and sodium nitrate
h) sodium acetate and sodium nitrite
i) potassium acetate and potassium laurate
j) calcium acetate and calcium propionate

8. Two monobromo derivatives of compound *A* are theoretically possible. When 0.1000 g. of *A* was added to 25.00 ml. of 0.1 *N* sodium hydroxide, 13.7ml. of 0.1 *N* hydrochloric acid was required to bring the solution to neutrality. What was the neutralization equivalent of *A*? Write the structure of *A*.

9. Liquid compound *A* is only slightly soluble in water. The aqueous solution turns blue litmus red and does not decolorize bromine water. When a mixture of *A*, water, and calcium carbonate was heated and stirred, some of the solid dissolved. From the clear solution a solid, *B* was obtained by concentration and cooling. After drying, *B* was found to contain 14.8% calcium. Write a possible structure for *A*.

10. Liquid compound *A* does not seem to dissolve when shaken with water. The aqueous solution, however, reddens blue litmus. *A* dissolves in aqueous sodium hydroxide. When 0.2000 g. of *A* was added to 25.00 ml. of 0.1 *N* sodium hydroxide, 10.0 ml. of 0.1 *N* hydrochloric acid was required to bring the solution to neutrality. What was the neutralization equivalent? Write a possible structure for *A*.

11. Show how to calculate ΔH for the gas phase reaction of the formation of:

a) acetic acid from acetaldehyde
b) acetic acid from acetonitrile
c) ethyl acetate from acetic acid
d) acetic anhydride from acetic acid
f) acetamide from acetic acid
g) chloroacetic acid from acetic acid
h) bromoacetic acid from acetic acid
i) carbon monoxide from formic acid

CHAPTER 13

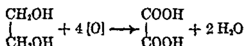
Dicarboxylic Acids

When a molecule has two carboxyl groups, the compound is a dibasic acid, and each carboxylic group reacts more or less independently of the other, although in the first two members, oxalic acid and malonic acid, there is a noticeable influence of the one upon the other.

With the exception of the first member, oxalic acid, these acids may be defined as the dicarboxyl substitution products of the hydrocarbons just as the glycols are the dihydroxy substitution products. Oxalic acid, in which two carboxyl groups are directly joined to each other, may be expected to have properties different from the other acids since it does not come under this definition.

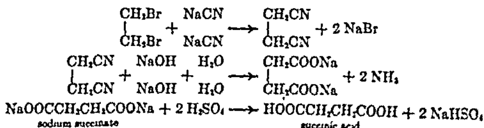
Synthesis of Dicarboxylic Acids. The first two methods below are general methods.

1. *From dihydric primary alcohols*, by oxidation.

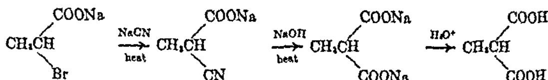


This reaction shows the relationship of this class of acids to the glycols, but is of little importance as a synthetic method since the glycols of this type, with the exception of ethylene glycol, usually are not as readily available as the acids.

2. *From α,ω-dibromoalkanes* (bromine attached to terminal carbon atoms), by means of the nitrile synthesis.



3. *From α-bromoacids.* These, in the form of salts, may react, as in the nitrile synthesis. The products are substituted malonic acids. Chloroacetic acid can be converted into malonic acid.



4. *From potassium salts of half esters of dibasic acids,* by electrolysis.



$$2\ ROOC(CH_2)_nCOO^- - 2e^- \longrightarrow ROOC(CH_2)_{2n}COOR + 2\ CO_2$$

This reaction is analogous to the production of ethane by the electrolysis of an aqueous solution containing acetate ion (p. 45). In this reaction the intermediate free radical, $ROOC(CH_2)_nCOO\cdot$, decomposes to carbon dioxide and a second free radical, $ROOC(CH_2)_n\cdot$; two of the latter then combine to form a molecule of the final product, the ester of a different dibasic acid. The ester formed by the electrolysis reaction may be saponified with a base and the dibasic acid may be obtained by acidification. This is a general method for obtaining dicarboxylic acids of an even number of carbon atoms, but often the yields are low.

5. *From malonic ester.* One of the most convenient methods of synthesizing monoalkylated and dialkylated malonic acids, $RCH(COOH)_2$ and $R_2C(COOH)_2$ starts with ethyl malonate (Chap. 19).

Nomenclature. The dicarboxylic acids may be called by their common names (see Table 46) or named as acid derivatives of hydrocarbons. In the latter case the longest chain containing the carboxyl groups is picked out and designated by name. This is followed by the word "diacid." In still another system, which is preferable, the carboxyl group is looked upon as a substituent, much like chlorine or hydroxyl. Succinic acid, $HOOCCH_2CH_2COOH$, is either butanediacid or 1,2-ethanedicarboxylic acid or 1,2-dicarboxyethane; glutaric acid, $HOOCCH_2CH_2CH_2COOH$, is pentanediacid or 1,3-propanedicarboxylic acid or 1,3-dicarboxypropane.

Properties of the Series. In Table 46 are listed the most important of the *alpha,omega*-series of dicarboxylic acids and their physical properties. In this series the carbon atoms of the carboxyl groups constitute the terminal atoms of normal chains. Solubility in ether is remarkably low for compounds having such a large number of carbon atoms. For the lower members this is due to the high oxygen-to-carbon ratio and to the high melting points. Here also the acids of lower melting point in general have higher solubilities.

The melting points and solubilities in water are plotted together to show that the acids with an odd number of carbon atoms have the higher solubilities and the lower melting points (Fig. 12). The melting point curve of the acids having an even number of carbon atoms has a downward trend, and that of the odd-numbered acids, except malonic, has an upward trend. It has already been noted in the case of the monobasic acids that the even-numbered members have the higher melting points. In other homologous series also the curves of the melting points have a zigzag appearance with the even-numbered members higher. The dibasic acids with more than three carbon atoms can be distilled without decomposition under reduced pressure, but the first two members decompose. At atmospheric pressure and high temperatures the third and fourth members lose water to form anhydrides.

TABLE 46 | Constants of Some α,ω-Dicarboxylic Acids

ACID		M.P. °C	B.P. °C	SOLUBILITY G./100 G. IN		K_1	K_2	HEAT OF COMB., C_p KCAL. PER MOLE
name	formula			H_2O at 20°	Et_2O at 15°			
Oxalic	HOOC—COOH	189	sublm.	9.52 [a]	1.3	3.5×10^{-2}		60.2
Malonic	$HOOCCH_2COOH$	136 [d]	>140 [d]	73.5	8	1.4×10^{-3}	2.2×10^{-6}	
[illegible]	[illegible]	[illegible]	234 [d]	6 9	1.2	6.4×10^{-5}	$2 5\times10^{-6}$	
[illegible]	[illegible]	[illegible]	304	83 0		4.5×10^{-5}	3.8×10^{-6}	
[illegible]	[illegible]	[illegible]	265 [b,c]	1.44 [e]	0 6	3.7×10^{-5}	2.4×10^{-6}	668.6
[illegible]	[illegible]	[illegible]	272 [b,f]	5.0		3.4×10^{-5}	2.6×10^{-6}	
[illegible]	[illegible]	[illegible]	279 [b,g]	0.16	.8	2.6×10^{-5}	$2 5\times10^{-6}$	982.8
[illegible]	[illegible]	[illegible]	287 [b,h]	.24	2.7	$2 9\times10^{-5}$	$2 8\times10^{-6}$	1140 1
[illegible]	[illegible]	[illegible]	294 [b,i]	.1	sol.	2.6×10^{-5}	$2 6\times10^{-6}$	1297.3

[a] As the dihydrate. [b] At 100 mm. [c] 205° at 10 mm. [d] Decomposes. [e] At 15°. [f] 212° at 10 mm. [g] 219° at 10 mm. [h] 226° at 10 mm. [i] 232° at 10 mm.

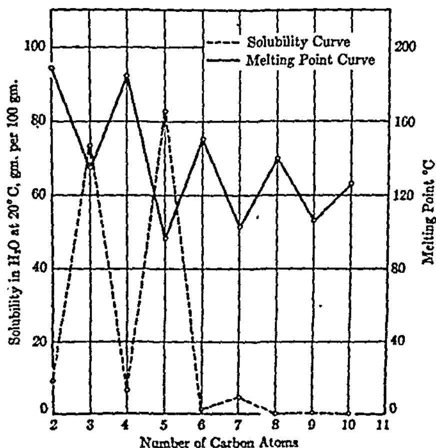
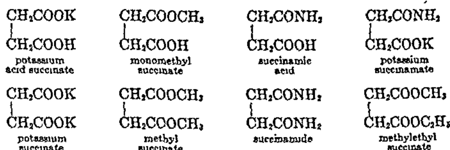


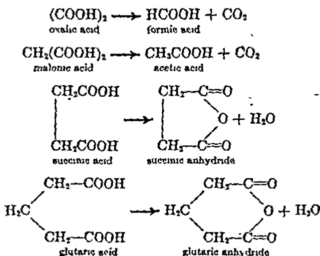
Figure 12 • Melting Points and Solubilities of Dicarboxylic Acids

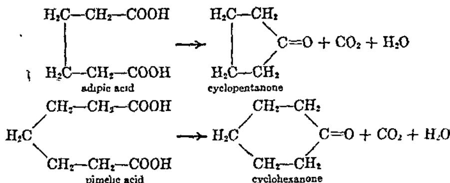
The primary ionization constants, K_1, drop rapidly from the first to the third members and more slowly from there on. The secondary, K_2, have essentially the same values with the exception of oxalic acid. The similar effect of the chloro and carboxyl groups in the α-position on the ionization of acetic acid is indicated by the respective values of 1.55×10^{-3} and 1.4×10^{-3} for α-chloroacetic and malonic acids respectively, and in the β-position on the ionization of propionic acid by the values of 8.6×10^{-5} and 6.4×10^{-5} for β-chloropropionic and succinic acids respectively.

General Reactions. The two functional groups of a dibasic acid in general react independently of each other. Thus the acids form two series of salts, *viz.*, neutral salts and acid salts. Also they form two series of esters and amides, and different combinations of these. Some of the possibilities are shown in the case of succinic acid below.



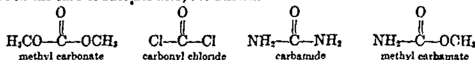
Effect of Heating Dicarboxylic Acids. These acids differ markedly in the way they decompose at higher temperatures. Oxalic and malonic acids undergo decarboxylation, with the formation of formic and acetic acid, respectively; succinic and glutaric acids undergo dehydration with the formation of succinic and glutaric anhydrides, respectively; while adipic and pimelic acids undergo elimination of carbonic acid with formation of cyclopentanone and cyclohexanone, respectively. For promoting the formation of cyclic ketones, the addition of manganous carbonate, or other compound which promotes ketone formation, is desirable (p. 177).



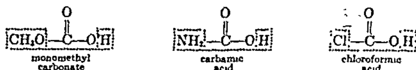


It is significant that the cyclic compounds formed in the above reactions contain rings of either five or six atoms. When rings of this size cannot be formed, the reaction may take a different course. The nature of side reactions in the above cases, and the reactions of higher acids when heated, are discussed later under higher acids. The likelihood that rings of five and six atoms will form is closely related to bond angle values (Table 13 and Chap. 7), and is opposed by the tendency of long carbon chains to assume orientations that make ring closure more difficult.

Carbonic Acid, HO—CO—OH. Although this is a dibasic acid, it is not a dicarboxylic acid. Carbonic acid has never been isolated, owing to the fact that it is unstable. It is mentioned here because many derivatives, similar to those listed above in the case of succinic acid, are known.

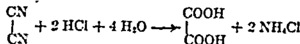


Not only carbonic acid but also many other theoretically possible derivatives do not exist. In general, compounds are unstable when certain pairs of radicals are attached to a carbon atom, *viz.*, OH and OH, OH and OR, OH and NH_2, OH and halogen. Thus the following derivatives of carbonic acid do not exist, for they decompose in the manner indicated, forming carbon dioxide.



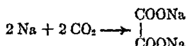
Oxalic Acid, $(COOH)_2$. This acid occurs in sorrel (*Oxalis*) as the acid potassium salt. This compound was first observed at the beginning of the seventeenth century and thus is one of the longest known naturally occurring organic compounds. The acid occurs also in rhubarb, in the leaves of the sugar beet, and in a large number of other plants. Usually it is present as a salt. Small quantities of calcium oxalate are present in the urine of man and animals.

Oxalic acid may be prepared by the oxidation of glycol (p. 160) or by the acid-catalyzed hydrolysis of cyanogen, methods of theoretical interest mainly.



It is often prepared by heating cane sugar with an excess of nitric acid. Other carbohydrates, for example, starches and other sugars, usually can be oxidized so as to yield some oxalic acid.

Sodium oxalate is produced by the rapid heating of sodium formate (p. 180), by the action of dry carbon dioxide on sodium metal at 360°, or from sawdust.



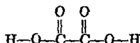
When cellulosic material, for example, sawdust, is heated with sodium hydroxide at 250 to 300°, sodium oxalate is formed. This is extracted by hot water and may be recovered as such by crystallization. Calcium oxalate may be obtained by precipitation with milk of lime. This salt is digested with dilute sulfuric acid in correct amount, calcium sulfate is removed, and oxalic acid is crystallized from the solution.

Oxalic acid is produced directly from glucose by a fermentation process, the oxalic acid fermentation. This is induced by the mold *Aspergillus niger* in a nutrient solution containing glucose. Citric acid also is produced by this organism. Under optimum conditions, *i.e.*, a temperature of 15 to 20° and the presence of calcium carbonate, which prevents the pH from dropping too low, about half of the sugar is converted into oxalic acid.

Oxalic acid crystallizes with two molecules of water which may be driven off by heating at 100°. Some oxalic acid sublimes at the same time. Oxalic acid and the soluble salts are poisonous. The best antidote is milk of lime, next best a suspension of precipitated calcium carbonate in water.

Oxalic acid forms two series of salts, *viz.*, acid salts and neutral salts. The acid salts are the less soluble in water. The neutral ammonium salt is much used in analysis, for it quantitatively precipitates calcium ion as insoluble calcium oxalate. Oxalic acid is used as a bleaching agent, especially for straw and flax. Acid salts are useful in removing stains due to iron rust or to an iron ink. This is ascribed to the tendency of iron to form complex ferrioxalate ions.

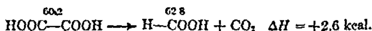
The structure of the oxalic acid molecule is shown below.



A carbon-to-carbon bond is indicated by two methods of synthesis, *viz.*, the oxidation of glycol and hydrolysis of cyanogen (see above). The two carboxyl groups have the usual structure.

Reactions of Oxalic Acid. Oxalic acid forms two series of salts, esters, amides, etc., as do succinic acid and other dibasic acids (p. 188).

1. *Pyrolysis.* When heated to about 150° or higher, oxalic acid undergoes decarboxylation.



The reaction is slightly endothermic on the basis of heats of combustion. As a method of preparing formic acid, the process is not very satisfactory, since much oxalic acid sublimes and some of the formic acid decomposes. However, addition of glycerol leads to a good preparative method. Oxalic acid decomposes smoothly in glycerol solution, through the intermediate formation of glycerol esters of oxalic and formic acids (see Glycerol Oxalate, p. 250).

When heated with concentrated sulfuric acid, oxalic acid decomposes to carbon dioxide, carbon monoxide, and water, for under these conditions formic acid also decomposes readily.



$$(COOH)_2 \longrightarrow CO_2 + CO + H_2O$$

This reaction sometimes is used as a source of carbon monoxide but is not as satisfactory as the decomposition of formic acid, because of the presence of carbon dioxide. When an aqueous solution of oxalic acid containing a soluble uranium salt is illuminated by sunlight or arc light, decomposition to carbon dioxide and carbon monoxide takes place.

2. *Oxidation.* Potassium permanganate in aqueous acid solution quantitatively oxidizes oxalic acid to carbonic acid.



$$(COOH)_2 + [O] \longrightarrow 2\,CO_2 + H_2O$$

Manganous ion accelerates the reaction. Oxalic acid or a salt often is used for standardizing permanganate solution. For this purpose potassium tetroxalate, $KH_3(C_2O_4)_2 \cdot 2\,H_2O$, has the advantage that it does not lose water of crystallization when dried. Dichromate in acid solution also oxidizes oxalic acid. Permanganate in basic solution does not oxidize oxalate ion, even when heated.

Scission of Carbon-to-Carbon Bonds. The ready degradation of oxalic acid when heated or subjected to oxidation indicates that loading of adjacent carbon atoms with oxygen atoms makes the bond between the carbon atoms more susceptible to rupture than a carbon-to-carbon bond in a hydrocarbon. Other electronegative atoms or radicals, for example, chlorine atoms and nitro groups, exert similar effects (refer to Trichloroacetic Acid, p. 206).

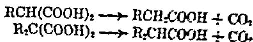
Malonic Acid, Methanedicarboxylic Acid, $CH_2(COOH)_2$. This occurs as the calcium salt in the sugar beet. It was discovered as the result of the oxidation of malic acid. Oxalacetic acid, the first oxidation product, is also oxidized, with scission of a carbon-to-carbon bond.



$$\underset{\text{malic acid}}{HOOCCH_2CHOHCOOH} \longrightarrow \underset{\text{oxalacetic acid}}{HOOCCH_2COCOOH} \longrightarrow \underset{\text{malonic acid}}{HOOCCH_2COOH} + CO_2$$

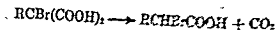
Malonic acid can be obtained from ethyl malonate by saponification, followed by decomposition of the resulting salt with dilute aqueous sulfuric acid and extraction of the solution with ether.

Four interesting reactions of malonic acid are decarboxylation, halogenation, condensation, and formation of carbon suboxide. Malonic acid decomposes to acetic acid and carbon dioxide when heated alone above its melting point, or when its saturated aqueous solution is heated to 68°. Derivatives of malonic acid decompose similarly. *This is a step in the important synthesis of monocarboxylic acids by means of the malonic ester synthesis* (Chap. 19). Thus a monoalkylated malonic acid yields a monoalkylated acetic acid, and a dialkylated malonic acid yields a dialkylated acetic acid.



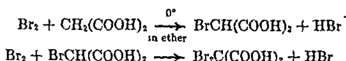
$$RCH(COOH)_2 \longrightarrow RCH_2COOH + CO_2$$
$$R_2C(COOH)_2 \longrightarrow R_2CHCOOH + CO_2$$

Likewise, an α-chloro- or bromomalonic acid yields the corresponding α-chloro- or bromo-fatty acid.



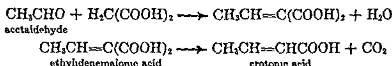
$$RCBr(COOH)_2 \longrightarrow RCHBrCOOH + CO_2$$

The methylene hydrogen atoms of malonic acid, because of the activating influence of the two carboxyl groups, are more reactive than the *alpha*-hydrogen atoms of a monocarboxylic acid. Malonic acid is smoothly brominated to bromomalonic and dibromomalonic acids.



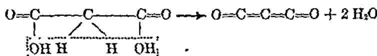
It will be recalled that acetic acid reacts only slowly with bromine, even when a catalyst (phosphorus tribromide) is present.

Malonic acid reacts with acetaldehyde or other aldehyde, preferably in the presence of an organic base (*e.g.*, piperidine), to produce an unsaturated monobasic acid. The change involves more than one reaction.

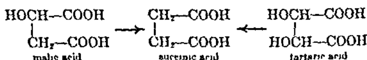


Two reactions are believed to be involved in the formation of ethylidenemalonic acid; the first, a condensation similar to an aldol condensation (Chap. 17); the second, elimination of a molecule of water. A third reaction is decarboxylation of ethylidenemalonic acid to crotonic acid.

Carbon suboxide, C_3O_2, is formed when malonic acid is heated with phosphorus pentoxide. Two molecules of water are eliminated from one molecule of malonic acid.

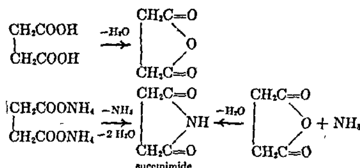


Succinic Acid, Ethane-1,2-dicarboxylic Acid, $(CH_2COOH)_2$. This acid is found in amber (L. *succinum*, amber), in lignite, and in many fossil woods. It is present also in many plants. It is formed in small amount during alcoholic fermentation of sugar by yeast. Succinic acid is obtained as a by-product in the production of colophony by distillation of amber, and is produced during fermentation of malic or tartaric acid by certain molds or bacteria. In this fermentation process the alcoholic hydroxyl groups of these acids are reduced.



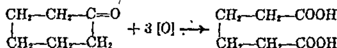
The reduction of these acids to succinic acid can be accomplished experimentally by heating with hydriodic acid at temperatures of 120 to 130°.

Succinic acid can be synthesized from ethylene bromide (p. 121). Like other dibasic acids it forms two series of derivatives (p. 188). An interesting reaction is the formation of a cyclic anhydride, succinic anhydride, when heated. Another is the formation of succinimide, a cyclic imide, by heating ammonium succinate, or by passing ammonia over heated succinic anhydride.



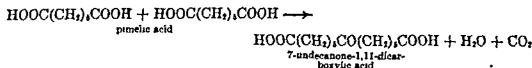
In general, acids do not easily form anhydrides simply by heating, but require the presence of a strongly dehydrating agent. The ease of formation of succinic anhydride and succinimide is connected with the ease of formation of five-membered rings (Chap. 7).

Higher Acids. Of the higher dibasic acids, adipic acid is the most important. It is produced on a large scale by the oxidation of cyclohexane or cyclohexanol, usually high temperature oxidations with air over a catalyst (vanadium pentoxide, etc.). The cyclohexane ring is opened, with oxidation of terminal carbon atoms to carboxyl groups (Chap. 26). In the laboratory, adipic acid is readily obtained by the oxidation of cyclohexanone with nitric acid.



Adipic acid is utilized in the manufacture of nylon (Chap. 22).

Glutaric acid, $CH_2(CH_2COOH)_2$, when heated yields glutaric anhydride; adipic acid, $(CH_2CH_2COOH)_2$, yields cyclopentanone; and pimelic acid, $CH_2(CH_2CH_2COOH)_2$, yields cyclohexanone (p. 189). A side reaction takes place between two molecules.



Once the bimolecular reaction has taken place, cyclization, by reaction between the terminal carboxyl groups, is even less likely to occur. However, reaction can take place with another molecule of dibasic acid. In the case of pimelic acid, the compound from three molecules has a normal chain of nineteen carbon atoms. The reaction can continue The final result is a polyketonic acid having a high molecular weight and a long carbon chain. The reaction product actually is a mixture of compounds of different complexities. Thus the polymeric reaction can accompany the cyclization reaction. Even in the cyclization which takes place the most readily, *viz.*, the formation of cyclopentanone from adipic acid, some polymer is formed.

The polymeric reaction is the main reaction when azelaic acid or a higher acid undergoes decarboxylation when heated. The products are linear polyketonic compounds of high molecular weight.

PROBLEMS

1. Show how the following may be obtained by the oxidation of a glycol:

a) succinic acid
b) glutaric acid
c) adipic acid
d) methylmalonic acid
e) ethylmalonic acid
f) *n*-propylmalonic acid
g) methylsuccinic acid
h) ethylsuccinic acid

2. Show how the following may be obtained from a glycol but not by an oxidation reaction:

a) succinic acid
b) glutaric acid
c) adipic acid
d) methylsuccinic acid
e) ethylsuccinic acid
f) α,α'-dimethylsuccinic acid
g) β-methylglutaric acid
h) β-ethylglutaric acid

3. Show how the following may be obtained from a fatty acid:

a) ethylmalonic acid
b) *n*-propylmalonic acid
c) *n*-butylmalonic acid
d) isobutylmalonic acid

4. Show how the following may be obtained from another dibasic acid:

a) succinic acid
b) adipic acid
c) suberic acid
d) sebacic acid

5. Write the structural formula of a dibasic acid which is easily converted into:

a) *n*-butyric acid
b) isobutyric acid
c) *n*-valeric acid
d) α-methyl-*n*-butyric acid
e) isovaleric acid
f) α,β-dimethylbutyric acid
g) β,γ-dimethylvaleric acid
h) α-bromo-*n*-valeric acid
i) α-chloroisovaleric acid
j) α-chloro-*n*-caproic acid

6. *Show how the following could be separated so that one component is recovered* to the extent of at least 90%, and reasonably free of the other component:

a) glutaric acid and heptadecane
b) glutaric acid and suberic acid
c) suberic acid and heptadecane
d) adipic acid and caprylic acid
e) adipic acid and tetramethylene glycol
f) malonic acid and *n*-amyl alcohol
g) oxalic acid and *n*-butyl alcohol
h) oxalic acid and formic acid

7. Describe a convenient chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) oxalic acid and formic acid
b) oxalic acid and acetic acid
c) oxalic acid and caproic acid
d) malonic acid and formic acid
e) malonic acid and acetic acid
f) malonic acid and dimethylmalonic acid
g) malonic acid and succinic acid
h) methylmalonic acid and methylsuccinic acid
i) ethylmalonic acid and methylsuccinic acid
j) dimethylmalonic acid and methylsuccinic acid

8. Write a possible structure for each of the compounds involved in the following changes:

a) compound *A*, $C_{[illegible]}H_{[illegible]}O_4$, when heated, is converted into compound *B*, $C_{[illegible]}H_{[illegible]}O_{[illegible]}$.
b) compound *A*, $C_{[illegible]}H_{[illegible]}O_4$, when heated, is converted into compound *B*, $C_{[illegible]}H_{[illegible]}O_{[illegible]}$.
c) compound *A*, $C_{[illegible]}H_{[illegible]}O_4$, when heated, is converted into compound *B*, $C_{[illegible]}H_{[illegible]}O_{[illegible]}$.
d) compound *A*, $C_{[illegible]}H_{[illegible]}O_4$, when heated, is converted into compound *B*, $C_{[illegible]}H_{[illegible]}O_{[illegible]}$.

CHAPTER 14

Unsaturated and Halogenated Acids

UNSATURATED ACIDS

Unsaturated monocarboxylic acids may be regarded as unsaturated hydrocarbons in which one hydrogen atom of the hydrocarbon has been replaced by one carboxyl group. Thus from ethylene, I, one unsaturated acid, II, is possible, and from propylene, III, three structurally isomeric acids, IV, V, and VI, are possible. All are known.


ethylene
I


acrylic acid
II


propylene
III


vinylacetic acid
IV


methylacrylic acid
(methacrylic acid)
V


crotonic acid
isocrotonic acid
VI

In addition there are two stereoisomers having structure VI. The number of isomeric forms of higher acids mounts rapidly. Thus the number of isomeric unsaturated acids is greater than that of saturated acids of the same number of carbon atoms.

Unsaturated acids are of interest on account of their occurrence in natural products, their tendency to polymerize, and the importance of stereoisomerism.

Nomenclature. The more common of the unsaturated acids usually are known by the common (trivial) names, as listed in Table 47, page 196. Generally they are listed under these names in *Chemical Abstracts*. The higher acids sometimes are named as derivatives of the lower acids, and the positions occupied by side chains are indicated by Greek letters. In the modified I.U.C. system used by *Chemical Abstracts*, the unsaturated carbon chain containing the carboxyl group is selected. The acid is named by changing to -enoic the ending -ene of the unsaturated hydrocarbon of the same number of carbon atoms, and adding the word acid. The position of the double bond is indicated by a Greek letter according to the method of indicating substituents in fatty acids. Thus VII is α-methyl-β-vinylpropionic acid, or α-methyl-γ-pentenoic acid. In the case of dibasic or polybasic acids, the acid sometimes is named as a carboxyl derivative of an unsaturated hydrocarbon,

according to the I.U.C. system. Thus muconic acid, VIII, is 1,3-butadiene-1,4-dicarboxylic acid

$$\underset{\text{VII}}{CH_2{=}CHCH_2CH(CH_3)COOH} \qquad \underset{\text{VIII}}{HOOCCH{=}CHCH{=}CHCOOH}$$

Sometimes the position of the double bond is indicated by two Greek letters, which correspond to the two carbon atoms which the double bond joins; for example, VII is α-methyl-γ,δ-pentenoic acid.

TABLE 47 **Properties of Some Unsaturated Acids**

NAME	FORMULA	M.P. °C	B.P. °C
Acrylic	$CH_2{=}CHCOOH$	12.3	141.9
Isocrotonic	$CH_3CH{=}CHCOOH$	15.5	172 [d]
Crotonic	$CH_3CH{=}CHCOOH$	72	189
Vinylacetic	$CH_2{=}CHCH_2COOH$	−39	163
Methacrylic	$CH_2{=}C(CH_3)COOH$	15–16	161–163
Angelic	[illegible]	45 5	185
Tiglic		64.0	198
Oleic		16	223^{10}
Elaidic		44	225^{10}
Erucic		34	281^{30}
Brassidic		61.5	282^{30}
Sorbic		134	228 [d]
Linoleic		−11	$229\text{–}230^{16}$
Linolenic			$230\text{–}232^{17}$
Propiolic		18	144 [d]
Maleic	$HOOCCH{=}CHCOOH$	130.5	
Fumaric	$HOOCCH{=}CHCOOH$	302	
Muconic	$HOOCCH{=}CHCH{=}CHCOOH$	307 [d]	
Traumatic	$HOOC(CH_2)_8CH{=}CHCOOH$	166	
Maleic anhydride	$OCCH{=}CHCO$ (with —O— bridging the two CO groups)	60	202 [e]

[d] Decomposes. [e] Sublimes.

[10] A superior figure shows the pressure in millimeters under which the compound boils at the temperature stated.

General Methods of Preparation. Unsaturated acids may be obtained by some of the general methods of preparing saturated acids (p. 173).

1. *From unsaturated aldehydes by oxidation* with reagents that do not attack the double bond, as for example, silver oxide.

$$\underset{\text{acrolein}}{CH_2{=}CH{-}CHO} + Ag_2O \longrightarrow \underset{\text{acrylic acid}}{CH_2{=}CH{-}COOH} + 2\,Ag$$

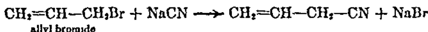
Hydrogen peroxide under basic conditions usually is satisfactory also.

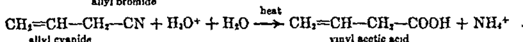
2. *From esters of unsaturated acids, by saponification and acidification*

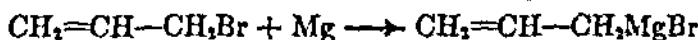
$$CH_2{=}CH{-}COOCH_3 + NaOH \longrightarrow CH_2{=}CH{-}COONa + CH_3OH$$
$$CH_2{=}CH{-}COONa + H_2SO_4 \longrightarrow CH_2{=}CH{-}COOH + NaHSO_4$$

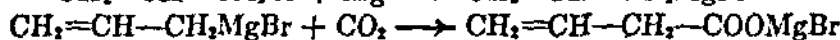
Esters of some unsaturated acids are produced commercially for polymerization purposes (see unsaturated esters, p. 229). A disadvantage of this method, in the case of higher acids, is the tendency of the double bond to shift under alkaline conditions.

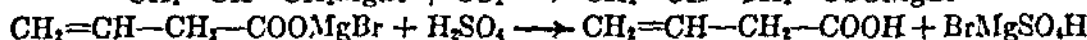
3. *From allyl type halides*, via the nitrile or Grignard synthesis.









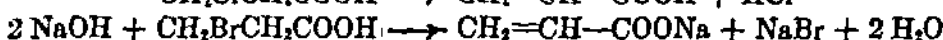


A disadvantage of the Grignard method is the pronounced tendency of the Grignard reagent to couple with an allyl type halide. This can be obviated by the proper cycling technique.

In addition to the above general methods, *alpha*-unsaturated acids may be obtained by other methods.

4. *From β-halogenoacids*, sometimes by heating alone, but preferably by heating with bases.

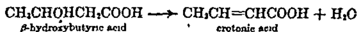


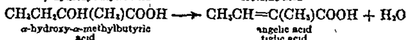


5. *From α,β-dibromoacids*, by heating with metallic zinc.

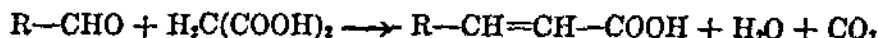


6. *From hydroxy acids.* β-Hydroxy acids usually decompose slowly when heated; the reaction is promoted by the presence of a suitable acidic catalyst, for example, sodium bisulfate; α-hydroxy acids sometimes decompose when heated with a suitable catalyst, for example, aluminum oxide.

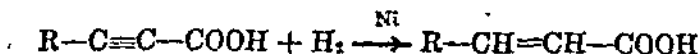




7. *By condensation of aldehydes with malonic acid* in the presence of piperidine (p. 192).



8. *By controlled hydrogenation of alkyne acids.*



Reactions of Unsaturated Acids. They undergo the usual reactions of acids, for example, rapid neutralization of bases and formation of esters, acid chlorides, anhydrides, and amides. Also they undergo the typical reactions

of olefins. Thus unsaturated acids display a multiplicity of chemical properties. There is some effect of one group upon the other. The double bond affects the carboxyl group most when in the *alpha*-position. It increases the acidity of the acid (propionic acid, 1.34×10^{-5}, acrylic acid, 5.6×10^{-5}) and has some effect in increasing the ease of decarboxylation.

The influence of the carboxyl group on reactions of the double bond is more important, especially when the double bond is in the *alpha*-position. This is shown by an increased ease of reduction, a decreased ease of addition of bromine, a mobility of the double bond under alkaline conditions, and the course of unsymmetrical addition.

1. *Reduction of the double bond.* In addition to hydrogenation methods, reduction takes place with sodium amalgam and water, with zinc and sulfuric acid, or with many other metals.



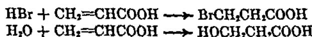
2. *Addition of bromine.* Bromine adds readily to acrylic acid and to other monobasic unsaturated acids. But in the case of fumaric acid, in which a carboxyl group is attached to each unsaturated carbon atom, bromine addition takes place slowly.

3. *Shifting of the double bond.* When vinylacetic acid is heated in aqueous basic solution, it is transformed in part to crotonic acid. Conversely, crotonic acid under similar treatment is partially converted to vinylacetic acid. The two acids, more specifically the respective anions, are in equilibrium with each other.



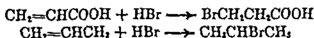
This shifting of the double bond between the α- and β-positions is general.

4. *Unsymmetrical addition.* Hydrogen bromide adds to acrylic acid, forming β-bromopropionic acid, and hydration takes place under basic conditions or slowly at 100° in dilute aqueous acid, to form β-hydroxypropionic acid (hydracrylic acid).



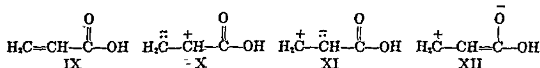
5. *Polymerization.* Higher unsaturated acids on exposure to air slowly darken and become more viscous. Linoleic acid, which has two double bonds, becomes quite hard. Other highly unsaturated acids, linolenic acid especially, also harden. This phenomenon is ordinarily known as "drying," and the liquids showing this behavior are called "drying oils." The change is due to polymerization, induced by oxygen. Esters of unsaturated acids polymerize more easily than the acids. Thus glycerides of higher unsaturated acids are much more important than the acids as drying oils (p. 246), and esters of the lower unsaturated acids, especially methyl acrylate and methyl methacrylate, are converted into synthetic resins (p. 230).

Unsymmetrical Addition to α-Unsaturated Acids. In the formation of β-bromopropionic acid and β-hydroxypropionic acid, mentioned above, the position taken by the negative radical is different from that taken in the normal addition reactions to propylene.



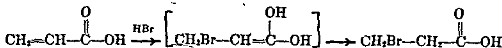
The carboxyl group is believed to influence the course of unsymmetrical addition through the operation of two effects, *viz.*, the inductive effect and the resonance (mesomeric) effect (p. 36). The strong dipole moment in the carbon-to-oxygen bonds of the carboxyl group induces a dipole moment, of smaller magnitude, however, in the carbon-to-carbon single bond, and this in turn induces a similar dipole moment in the double bond. The double bond has enhanced ionic character and the electrons of the bond are held more strongly by the *alpha*-carbon atom. Thus the *beta*-carbon is positive, relative to the *alpha*-carbon atom.

The carboxyl group influences the double bond more importantly, when it is in the *alpha,beta*-position, through the resonance effect. In this connection it is well to recall the explanation advanced for unsymmetrical addition to propylene (p. 72). For acrylic acid it is possible to write not only the three resonance forms, IX, X, and XI, which correspond to the three resonance forms of propylene, *viz.*, XX, XXI, and XXII, page 73, but also a fourth, XII, owing to the fact that the double bond is conjugated with the carboxyl group.

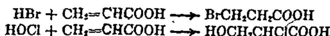


The last, XII, makes a very important contribution to the overall structure of the molecule, owing to its greater stability, relative to X and XI. The β-carbon atom therefore is positively charged, relative to the α-carbon atom. There are three other forms corresponding to IX, X, and XI, respectively, and in these each oxygen carries a formal charge, one positive, the other negative. However, the general relationships noted above are not significantly altered by these possibilities.

When unsymmetrical addition to acrylic acid takes place, the negative part of the addendum becomes attached to the positively charged β-carbon atom by 1,4-addition. The first product is unstable, and like enols (see Chap. 16) rearranges to the final stable product.



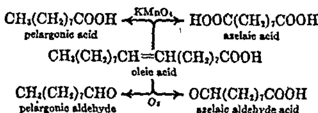
Thus when hydrogen bromide adds, it is the negative bromine atom which goes to the β-position, and when hypochlorous acid adds, it is the negative hydroxyl group which goes to the β-position.



If the double bond is located further away from the carboxyl group, as in the β,γ- or γ,δ-position, it is affected to a slight extent only by the carboxyl group, through the

inductive effect. The resonance effect is not operative, for the double bond no longer is conjugated with the carboxyl group

Structure Determination. The position of the double bond may be determined by oxidation with alkaline permanganate solution, or by ozonolysis. With normal chain compounds the carbon chain is broken at the position of the double bond. Permanganate causes oxidation to acids; ozone, if metallic zinc is present when the ozonide is decomposed with water, yields aldehydes. If an unsaturated carbon atom is tertiary, a ketone is formed. The determination of the structure of oleic acid, $C_{17}H_{33}COOH$, is a classical example of the application of these methods. Oleic acid with permanganate yields pelargonic and azelaic acids, and with ozone, pelargonic aldehyde and the half aldehyde of azelaic acid.



The results are in agreement and show that oleic acid has a normal carbon chain with the double bond between the two middle carbon atoms.

Occurrence of Unsaturated Acids. Crotonic acid is found in croton oil. Angelic acid occurs free in angelica root (*Angelica archangelica*), also as the amyl ester in Roman camomile oil. Tiglic acid has been isolated from the latter; it occurs in combination with glycerol in croton oil. Sorbic acid occurs in unripe berries of the mountain ash (*Sorbus*).

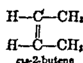
Oleic acid, in combination with glycerol, is an important constituent of most liquid or low melting edible oils and fats, for example, almond oil, coconut oil, corn oil, cottonseed oil, lard, linseed oil, and olive oil (the olive tree is *Olea europaea*). It is separated from other acids associated with it by ether extraction of the lead salts, prepared by the addition of a soluble lead salt to an aqueous solution of the potassium soap, obtained by saponification of the fat. Lead oleate is ether soluble, while the lead salts of saturated acids are not.

Erucic acid is present in cod-liver oil and mustard-seed oil as a glyceride. Traumatic acid has been isolated from bean sprouts. It stimulates the division and growth of plant cells. On this account it has been called a "wound hormone."

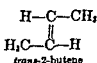
Linoleic acid, $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$, and linolenic acid, $CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$, are present as glycerides in linseed oil. Linoleic acid is an important constituent also of cottonseed, corn, and other vegetable oils These acids gradually harden when exposed to air, owing to a slow polymerization induced by oxygen. The presence of these acids in linseed oil is responsible for its property of "drying" (p. 246).

Stereoisomerism of Unsaturated Acids. Because there is restricted rotation about the double bond, stereoisomerism is possible when two dissimilar atoms or radicals are attached to each of the two unsaturated carbon atoms

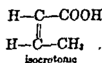
similar to the stereoisomerism of 2-butene (p. 64). In Table 47 are listed five pairs of geometrical isomers, *viz.*, isocrotonic and crotonic, angelic and tiglic, oleic and elaidic, erucic and brassidic, and maleic and fumaric acids. The similarity in structure of the members of each pair is shown by the products obtained on reduction of the double bond. Crotonic and isocrotonic acids both yield *n*-butyric acid, angelic and tiglic acids yield α-methyl-*n*-butyric acid, oleic and elaidic acids yield stearic acid, erucic and brassidic acids yield docosanoic acid, while maleic and fumaric acids yield succinic acid. The difference between isomerides is due to a different spatial arrangement about the double bond, as in the case of *cis*- and *trans*-2-butene, XIII and XIV, respectively. In XIII the two hydrogen atoms attached to the unsaturated carbon atoms lie on the same side of the double bond, and in XIV on opposite sides.



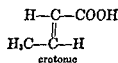
cis-2-butene
XIII



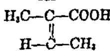
trans-2-butene
XIV



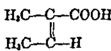
isocrotonic acid
XV



crotonic acid
XVI

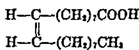


angelic acid
XVII

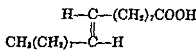


tiglic acid
XVIII

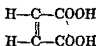
In isocrotonic acid, XV, the two hydrogen atoms lie on the same side of the double bond, while in crotonic acid, XVI, they are on opposite sides. Thus isocrotonic acid is the *cis*-isomer, and crotonic acid is the *trans*-isomer. Angelic acid, XVII, is *cis*, and tiglic acid, XVIII, is *trans;* oleic acid, XIX, is *cis*, elaidic acid, XX, is *trans;* maleic acid, XXI, is *cis*, fumaric acid, XXII, is *trans*.



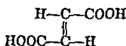
oleic acid
XIX



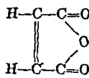
elaidic acid
XX



maleic acid
XXI



fumaric acid
XXII

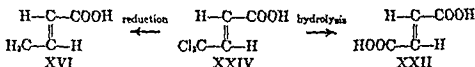


maleic anhydride
XXIII

Determination of Configuration. The spatial arrangement of atoms or groups in a stereoisomer is meant when reference is made to the configuration of the molecule. In the case of unsaturated molecules this means the location of atoms or groups in space about the two unsaturated carbon atoms (refer to *cis*- and *trans*-2-butene, p. 63). Only rarely is the configuration of a *cis*- or *trans*-isomer determined by a simple chemical test. The classical example is maleic acid. When maleic and fumaric acids are

separately heated, maleic acid, XXI, at 160° is converted into an anhydride, maleic anhydride, XXIII (p. 201); and fumaric acid, XXII, is converted into the same anhydride at 230°. The easy formation of the cyclic anhydride from maleic acid shows that it has the *cis*-configuration. Fumaric acid therefore has the *trans*-configuration.

The determination of the configuration of other pairs of geometrical isomers by chemical means usually presents greater difficulties. In some cases the compound can be related to maleic or fumaric acid. Thus crotonic acid, XVI, is related to fumaric acid, XXII, through *trans*-trichlorocrotonic acid, XXIV.



Physical methods often are applied to the problem of determining the configuration of geometrical isomers. The most generally useful constant is the electric dipole moment, which however is not usually applicable to acids, because the solutions are conducting. The *trans*-isomer always has the lower dipole moment, and in many cases has zero moment. Usually the *trans*-isomer also has the lower heat of combustion, higher melting point, lower solubility in solvents, and, when it is an acid, the lower ionization constant (Table 48). The boiling point relations are less general, for sometimes the *trans*-isomer has the lower boiling point (hydrocarbons), sometimes the higher (acids).

***cis,trans*-Isomerization.** Sometimes a geometrical isomer is observed to change to its stereoisomer. The relationship in the heats of combustion indicates that the *trans*-isomer is the more stable form at 25°, because ΔF is not greatly different from ΔH (p. 24). Also, at higher temperatures the equilibrium shifts in favor of the *cis*-isomer. Thus at room temperature and with the proper catalyst, a *cis*-isomer should change to a *trans*-isomer. Ordinarily an equilibrium would be expected, since the energy change is not large. The reaction in the case of maleic acid takes place easily, as when hydrochloric, hydrobromic, or hydriodic acid is added to an aqueous solution at room temperature. The slight solubility of fumaric acid (Table 48), aids in carry-

TABLE 48 | **Properties of Three Pairs of Geometrical Isomers**

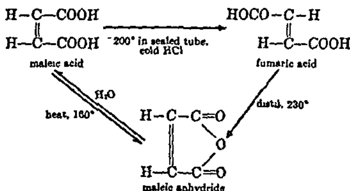
ACID	M.P. °C	B.P. °C	SP. GR.	SOLUBILITY IN		$K_1 \times 10^5$	$K_2 \times 10^5$	HEAT COMB. KCAL./MOLE
				H_2O	Et_2O			
Isocrotonic (*cis*)	15 5	172 [d]	1.027	40		3.6		486
Crotonic (*trans*)	72	189	0.964 [a]	8 [b]		2 15		478
Angelic (*cis*)	45.5	86 [c]	0.9539 [e]			5.0		635
Tiglic (*trans*)	64 0	95 [c]	0.9641 [e]			0.97		627
Maleic (*cis*)	130 5		1.590	78 8	8.19	1200	0 026	326
Fumaric (*trans*)	284		1.635	0 7	0 72	93	2.9	320

[a] At 79°. [b] At 19°. [c] At 12 mm. [d] Decomposes. [e] At 76°.

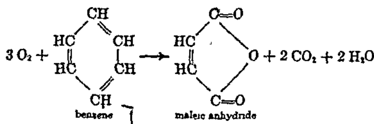
ing the reaction essentially to completion. Many *cis*-unsaturated acids change to *trans* by heating alone, or by heating with aqueous base. Oleic acid changes to elaidic acid in the presence of nitrous or phosphorous acid, or when heated with dilute nitric acid.

Isomerization of *cis,trans*-isomers to an equilibrium mixture can in general be accomplished in one or more ways as, for example, by heat alone or by the presence of acids, bases, or other catalytic substances, such as iodine. Illumination, especially with a small amount of iodine or bromine present, is one of the best ways, since foreign substances are not bothersome in the recovery and purification of the product. However, in this case energy is absorbed by the system. The effect is similar to a rise in temperature, with the result that at the final steady state attained by illumination at room temperature, the *cis*-form is present in higher percentage than in the thermal equilibrium mixture.

The maleic-fumaric system has the added feature of anhydride formation. Thus at sufficiently high temperature, where the rate of isomerization of *trans*- to *cis*-isomer is sufficiently great, and where also there is more of the *cis*-isomer than at room temperature, the equilibrium is disturbed by formation of the anhydride, which finally becomes the main reaction product.

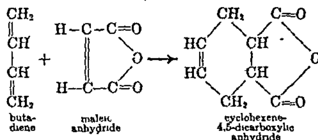


Maleic Anhydride. *This is an important compound from an industrial point of view.* It is manufactured from benzene (Chap. 27) by air oxidation over a vanadium pentoxide catalyst, and is obtained as a by-product in the air oxidation of naphthalene to phthalic anhydride.



It is used extensively in the manufacture of alkyd type synthetic resins, which are made by the reaction of dibasic acids with glycols and glycerol (p. 250).

An important reaction of maleic anhydride is the diene condensation (Diehls-Alder). Butadiene and other conjugated dienes react with many unsaturated compounds by 1,4-addition. The reaction with maleic anhydride is typical.



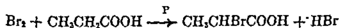
The presence of carbonyl groups in unsaturated compounds increases the tendency to react with dienes.

HALOGENATED ACIDS

Halogenated acids are acids in which one or more of the hydrogen atoms (attached to carbon) have been substituted by halogen. A monohalogenated acid contains two functional groups, *viz.*, the carboxyl group and the halogen atom, and thus displays a dual character, for it undergoes many of the reactions of alkyl halides, as well as those of acids. However, generally the properties are not strictly additive.

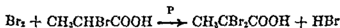
General Methods of Preparation. Either a halogen atom may be introduced into the molecule of an acid (methods 1, 2, 3, and 4 below), or the carboxyl group may be introduced into the molecule of a halogen compound (method 5). Direct substitution is the preferred method for α-halogenated acids.

1. *Halogenation of saturated acids.* Chlorine or bromine reacts with a monocarboxylic acid when heated in the presence of a suitable catalyst.



$$Br_2 + CH_3CH_2COOH \xrightarrow{P} CH_3CHBrCOOH + HBr$$

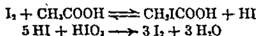
Phosphorus or a phosphorus halide often is added, sometimes sulfur or iodine. Sometimes ultraviolet radiation is effective. The product is an α-substituted acid. A second halogen atom can be introduced similarly into the *alpha*-position.



$$Br_2 + CH_3CHBrCOOH \xrightarrow{P} CH_3CBr_2COOH + HBr$$

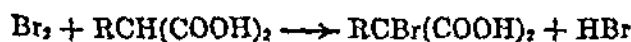
Chlorination of acids above acetic acid can be accomplished by means of sulfuryl chloride in the presence of benzoyl peroxide (see p. 178).

Iodination sometimes can be accomplished by the combined action of iodine and iodic acid. Iodine alone scarcely reacts with a saturated acid, for the energy change favors the reverse reaction (see p. 42). Iodic acid reacts exothermically with any hydrogen iodide formed by substitution, with the result that the overall reaction is exothermic.



$$I_2 + CH_3COOH \rightleftharpoons CH_2ICOOH + HI$$
$$5\,HI + HIO_3 \longrightarrow 3\,I_2 + 3\,H_2O$$

Malonic acid and substituted malonic acids react smoothly with chlorine or bromine in the absence of a catalyst (p. 192).

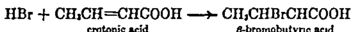


$$Br_2 + RCH(COOH)_2 \longrightarrow RCBr(COOH)_2 + HBr$$

This is a step in a convenient method of preparing α-halogenated acids, for the substituted malonic acid undergoes decarboxylation when heated.



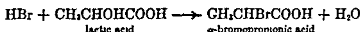
2. *Addition of hydrogen halides to unsaturated acids.* An α-unsaturated acid readily adds HX to form a β-halogenated acid (see p. 199).

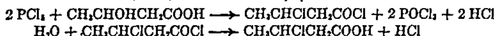


3. *Addition of chlorine or bromine to unsaturated acids.*

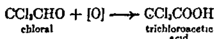


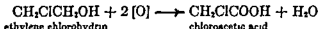
4. *Reaction of hydroxy acids with hydrobromic acid or with phosphorus pentachloride or bromide.*





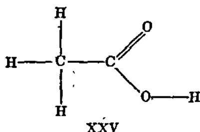
5. *Oxidation of halogenated aldehydes or halogenated primary alcohols.*



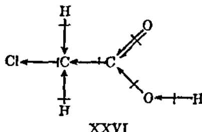


Reactions of Halogenated Acids. In general these acids undergo the typical reactions of the two functional groups, *viz.*, the carboxyl group and the halogeno group. However, the presence of one group modifies, to some extent, the reactivity of the other group. The relative positions of the two groups is important.

Influence of the halogen atom on the carboxyl group. The greatest influence of the halogen atom is the enhancement of the acidic nature of the carboxyl group. From the data of Table 49 it is evident that a chlorine, bromine, or iodine atom enhances the ionization constant of an acid to about the same extent, that the effect is greatest in the *alpha*-position, and that this effect drops off as the halogen atom is located further away from the carboxyl group. These relationships are explained on the basis of the inductive effect (p. 36). The bond dipole moment in a carbon-to-chlorine bond points away from the carbon atom, whereas in a carbon-to-hydrogen bond it points toward the carbon atom. Thus if the unsubstituted acid, XXV, is represented, for the sake of simplicity, as if it were devoid of any dipole moment, the effect of the



XXV



XXVI

chlorine atom in the chloroacid upon the bond dipole moment is shown schematically in XXVI, where the shorter distance between head and tail of the arrow indicates a smaller dipole moment. This shows that the hydrogen atom of the carboxyl group in XXVI is more positive than the one in XXV, since the stronger dipole in XXVI

TABLE 49 | Physical Constants of Some Halogenated Acids

NAME	M.P °C	B.P. °C	SP. GR. 20°/4°	K_a	SOLY. IN H_2O G./100 G.
Acetic [a]	16 60	118	1.049	1.76×10^{-5}	misc.
Chloroacetic	63; 56	189	1.58	1.55×10^{-3}	v. sol.
Dichloroacetic	11	194	1.563	5.14×10^{-2}	misc.
Trichloroacetic	59	196	1.62	9×10^{-1}	v. sol
Bromoacetic	50	208	1.93^{50}	1.38×10^{-3}	misc.
Iodoacetic	83			7.1×10^{-4}	sol
Propionic [a]	−22 0	141	0.992	1.34×10^{-5}	misc.
α-Chloropropionic	<−20	186	1.31^{0}	1.47×10^{-3}	misc
β-Chloropropionic	42	204		8.6×10^{-5}	v. sol.
α-Bromopropionic	25.7	203 5 [d]	1.700	1.08×10^{-3}	v. sol.
β-Bromopropionic	62 5			9.8×10^{-5}	v. sol.
Butyric [a]	−5.55	163 5	0.959	1.50×10^{-5}	misc.
α-Chlorobutyric		101^{14}		1.39×10^{-3}	s. sol.
β-Chlorobutyric	16 5	116^{22}	1.186	8.9×10^{-5}	
γ-Chlorobutyric	16	196^{22}	1.250^{10}	2.96×10^{-5}	s. sol.
α-Bromobutyric	−4	128^{24}	1.567	1.06×10^{-3}	6 6

[a] Included for reference [d] Decomposes.

indicates a higher degree of ionic character in the bond. Thus, the proton can ionize more easily. Also, it shows how the magnitude of the inductive effect drops off as it passes from atom to atom. This explains the diminished influence of the halogen atom as it is located further away from the carboxyl group, for with each additional methylene group, the inductive effect is divided among three bonds.

A substituent may exert an effect in other ways beside inductively, as for example, by means of resonance (probably not operative in the above case) or by mutual attraction or repulsion across space. The former is important in chelation (Chap. 19), the latter in steric hindrance (Chap. 35).

Another influence of the halogen atom is increased ease of decarboxylation. Trichloroacetic and tribromoacetic acids when heated are converted into chloroform and bromoform, respectively.



$$CCl_3COOH \longrightarrow CHCl_3 + CO_2$$

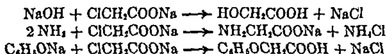


$$CBr_3COOH \longrightarrow CHBr_3 + CO_2$$

These reactions illustrate again the fact that an accumulation of negative radicals on adjacent carbon atoms makes the carbon-to-carbon bond more susceptible to rupture (p. 191).

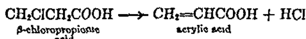
Influence of the carboxyl group on the reactivity of the halogen atom. When the halogen atom is in the *alpha*-position and when the acid is converted to a salt, displacement of

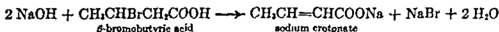
the halogen atom takes place more readily than when the halogen atom is part of an alkyl halide. Thus sodium chloroacetate reacts readily when heated with many compounds. Typical reactions are those with sodium hydroxide, ammonia, and sodium phenoxide to form hydroxyacetic, aminoacetic, and phenoxyacetic acids, respectively.



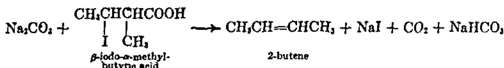
The enhanced reactivity of the chlorine atom in sodium chloroacetate is ascribed to the negative charge of the ion, which promotes the expulsion of the chlorine atom as chloride ion.

When the halogen atom is in the *beta*-position, the tendency is toward unsaturation. The unsaturated acid often results when the halogeno acid is heated alone or when it is heated with alkaline solution.

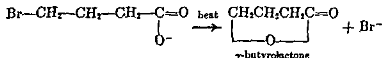




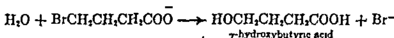
Sometimes decarboxylation also takes place. When solutions of the reactants below are mixed, decomposition proceeds spontaneously, and an unsaturated hydrocarbon is formed.



When the halogen atom is in the *gamma*-position, heating a salt of the acid leads to a lactone (inner ester of the corresponding hydroxy acid, Chap 18).



The corresponding γ-hydroxy acid is formed when the sodium salt is heated in aqueous solution.



PROBLEMS

1. Write equations for two syntheses of the following from compounds of fewer carbon atoms but of different types, making use of different synthetic methods, and passing through an unsaturated acid:

a) *n*-valeric acid
b) *n*-caproic acid
c) isocaproic acid
d) γ-methyl-*n*-valeric acid
e) δ-methyl-*n*-valeric acid
f) isocaprylic acid

2. Write the structure of a hydroxy acid which can be converted easily into the following, and indicate the reagent and steps:

a) acrylic acid
b) methacrylic acid
c) tiglic acid
d) sorbic acid
e) fumaric acid
f) α-pentenoic acid
g) α-hexenoic acid
h) α,β-dibromobutyric acid
i) α,β-dibromo-α-methylbutyric acid
j) α,β-dibromo-α-methylpropionic acid
k) α,β,γ,δ-tetrabromocaproic acid
l) α,β-dibromopropionic acid

3. Starting with crotyl alcohol, show the reaction steps which could be used in a practical laboratory preparation of:

a) crotonic acid
b) β-pentenoic acid
c) α,γ-hexadienoic acid
d) α-hexenoic acid

4. Describe a chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) isocrotonic and isobutyric acids
b) methacrylic and isobutyric acids
c) crotonic and maleic acids
d) crotonic and malonic acids
e) crotonic and oxalic acids
f) crotonic and *n*-butyric acids
g) vinylacetic and *n*-butyric acids
h) maleic and malonic acids
i) fumaric and succinic acids
j) acetic and chloroacetic acids
k) chloroacetic and trichloroacetic acids
l) bromoacetic and β-bromopropionic acids
m) propionic and β-iodopropionic acids
n) succinic and bromosuccinic acids
o) α-bromopropionic and α,β-dibromopropionic acids
p) β-bromopropionic and β-bromoacrylic acids

5. Write equations (with actual reagents) for the reactions involved in preparing the following, having ethyl alcohol as the only organic compound:

a) chloroacetic acid (*via* acetic acid)
b) chloroacetic acid (*via* other route)
c) α-chloropropionic acid
d) α-bromopropionic acid
e) 2-pentenoic acid
f) β-bromo-*n*-valeric acid
g) β-bromobutyric acid
h) α-bromobutyric acid.

6. Write the structure of a compound, $C_4H_6O_4$, which when heated is converted into $C_4H_4O_3$.

7. How many compounds, formula $C_4H_8O_3$, are rapidly converted into $C_4H_6O_2$ when heated?

8. Write the structure of an acid which when heated is converted into

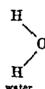
a) α-chloropropionic acid
b) chlorosuccinic acid
c) α-bromopropionic acid
d) α-chlorobutyric acid
e) α-bromo-isovaleric acid
f) dibromosuccinic acid

9. An organic compound gave negative qualitative tests for nitrogen, sulfur, and halogens. It was only very slightly soluble in water and in dilute aqueous acids, readily soluble in aqueous sodium carbonate. It rapidly reduced aqueous alkaline permanganate. From the reaction mixture, after an excess of permanganate had been added, oxalic and *n*-butyric acids were isolated. What was the compound?

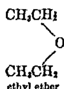
CHAPTER 15

Ethers, Esters, Anhydrides, and Acyl Halides

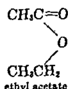
Ethers, esters, and anhydrides are structurally similar in that they are composed of two organic radicals attached to an oxygen atom. In ethers there are two alkyl radicals, in esters one alkyl and one acyl radical, and in anhydrides two acyl radicals. The relationship of the compounds to water can be shown by writing different organic radicals in place of the hydrogen atoms of the water molecule.



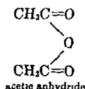
water



ethyl ether

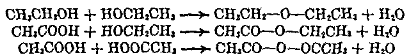


ethyl acetate



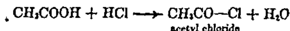
acetic anhydride

These three types of compounds may be regarded as anhydrides of the corresponding hydroxy compounds, and actually they can be obtained from them by the elimination of one molecule of water from two molecules of the hydroxy compounds.



$$CH_3CH_2OH + HOCH_2CH_3 \longrightarrow CH_3CH_2{-}O{-}CH_2CH_3 + H_2O$$
$$CH_3COOH + HOCH_2CH_3 \longrightarrow CH_3CO{-}O{-}CH_2CH_3 + H_2O$$
$$CH_3COOH + HOOCCH_3 \longrightarrow CH_3CO{-}O{-}OCCH_3 + H_2O$$

The formation of acetic anhydride from acetic acid does not proceed spontaneously. Phosphorus pentoxide or other powerful dehydrating agent is necessary, and yields even then are not good. Under these conditions it is possible also to bring about the formation of an acid chloride by the elimination of a molecule of water from an organic acid and hydrogen chloride.



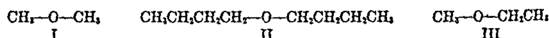
$$CH_3COOH + HCl \longrightarrow \underset{\text{acetyl chloride}}{CH_3CO{-}Cl} + H_2O$$

Thus acid chlorides can be regarded as anhydrides, actually mixed anhydrides of hydrogen chloride and a carboxylic acid.

There is a difference in the acid strength of the acids from which ethers, esters, anhydrides, and acid chlorides are derived. Ethyl alcohol is a very weak acid (10^{-20}), acetic acid is a weak acid (10^{-5}), and hydrochloric acid is

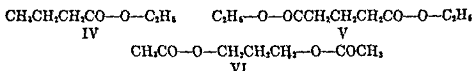
strong. These relationships are important in connection with the chemical reactivity of these four types of compounds, for they conform to the general pattern of anhydrides.

Nomenclature. Ethers are of two general types, *viz.*, symmetrical and unsymmetrical. Unsymmetrical ethers are indicated by the names of both radicals, symmetrical by the one radical, sometimes with the prefix *di-*.

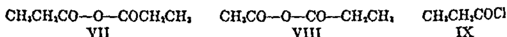


Thus I is methyl ether, II is *n*-butyl ether (sometimes dibutyl ether), and III is methyl ethyl ether.

Esters are named like salts, with the alkyl radical replacing the metal. In older literature the ethyl esters were called esters (or sometimes ethers) of the acid. Thus IV is ethyl butyrate, butyric ester, or (rarely) butyric ether, and V is ethyl glutarate or glutaric ester. With dihydric and polyhydric alcohols, usually the name of the alcohol is included. Thus VI is trimethylene glycol diacetate.



Anhydrides are of two general types, *viz.*, symmetrical and unsymmetrical, and are named like VII and VIII, which are propionic anhydride and acetic propionic anhydride, respectively. Acyl halides are named as halides of acyl radicals; IX is propionyl chloride.



In the I.U.C. system ethers are named as alkoxy derivatives of hydrocarbons, the larger radical being taken as the parent compound. Esters, anhydrides, and acid chlorides are named in relation to carboxylic acids. Thus I is methoxymethane, II is butoxybutane, and III is methoxyethane (not ethoxymethane); IV is ethyl butanoate or ethyl propanecarboxylate and V is diethyl 1,3-propanedicarboxylate; VII is propanoic anhydride; IX is propanoyl chloride.

Sometimes it is convenient to name esters as derivatives of hydrocarbons, either as acyloxy derivatives (similar to ethers, which are alkoxy derivatives) or as carbalkoxy derivatives (similar to acids, which are carboxy derivatives). Thus IV is butyroxyethane or carbethoxypropane, V is 1,3-dicarbethoxypropane, and VI is 1,3-diacetoxypropane. This method seldom is used for simple esters like IV, but may be quite useful with esters of polybasic acids or of polyhydric alcohols.

Inorganic Anhydrides. Two important generalizations can be made regarding inorganic acid anhydrides, including also mixed anhydrides of the acid halide type such as phosphorus pentachloride: (1) anhydrides of very

weak acids tend to be formed spontaneously from the acids by loss of water; (2) anhydrides of strong acids react exothermically and rapidly with water to form the acid or acids.

Examples of anhydrides that are formed spontaneously from weak acids are: CO_2 from H_2CO_3($K_a = 10^{-7}$ and 10^{-11}); Cl_2O from HOCl(10^{-10}); SO_2 from H_2SO_3(10^{-2} and 10^{-6}); N_2O_3 from HNO_2(10^{-4}); also, silica from silicic acid and alumina from aluminum hydroxide. Examples of anhydrides that react vigorously with water to form one or more molecules of strong acid are: PCl_3, PCl_5, P_2O_5, SO_3, SO_2Cl_2, Cl_2O_7. In a system consisting of water, an anhydride, and the corresponding acid (or acids), equilibrium conditions favor the formation of the anhydride if the acid is very weak, and of the acid if this is strong. These general relationships hold also in systems involving organic acids and anhydrides.

Preparation of Ethers, Esters, Anhydrides, and Acid Chlorides. Reactions listed for relatively simple compounds usually are slower the higher the molecular weight.

1. *Reaction between two molecules of* OH *compound (alike or dissimilar) to form water and an:*

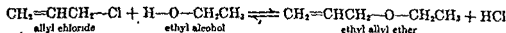
a) *Ether.* *This reaction has been described from the standpoint of rate, catalyst, and equilibrium* (p. 144).

b) *Ester.* When a mixture of ethyl alcohol and acetic acid stands at room temperature, a very slow reaction takes place, as shown by the fact that the acidity slowly decreases with a diminishing rate until, after some months, no additional change is observed. An equilibrium state is reached. The rate is markedly increased by the addition of a strong, anhydrous acid. Mixed vapors of the two reactants react only slowly up to 300°, but when passed over solid dehydrating catalysts, for example, thorium or titanium oxide at 150 to 300°, ethyl acetate is formed. The reaction is described in more detail under Esterification (p. 223).

c) *Acid anhydride or acid chloride.* Ordinarily water is not lost spontaneously when an acid, or a mixture of an organic acid with a hydrogen halide, is heated. The formation of an anhydride or an acid halide from a monocarboxylic acid by the action of a powerful dehydrating agent (p. 209) is of theoretical interest mainly. However, some dibasic acids form "inner" or cyclic anhydrides merely by heating (succinic acid, p. 188; maleic acid, p. 202).

2. *Reaction of an* OH *compound (the acid) with a halogen compound to form a hydrogen halide and an:*

a) *Ether.* This reaction has been observed when the halogen compound is very reactive, as with allyl chloride, but is not very common.



$$\underset{\text{allyl chloride}}{CH_2{=}CHCH_2{-}Cl} + \underset{\text{ethyl alcohol}}{H{-}O{-}CH_2CH_3} \rightleftharpoons \underset{\text{ethyl allyl ether}}{CH_2{=}CHCH_2{-}O{-}CH_2CH_3} + HCl$$

The reverse of a reaction of this type, especially with hydrobromic or hydriodic acid, is common.

b) *Ester.* A lower acyl halide reacts rapidly with a lower alcohol at room temperature.

$$\underset{\text{acetyl chloride}}{CH_3CO-Cl} + HOC_2H_5 \longrightarrow \underset{\text{ethyl acetate}}{CH_3CO-O-C_2H_5} + HCl$$

Primary and secondary alcohols react this way, but tertiary alcohols are converted to tertiary halides (however, see Relative Reactivities, p. 220). The reaction by which hydrogen chloride is eliminated between an acid, R—COOH and an alkyl halide, R—X, does not seem to take place. The reversal of this reaction especially with hydrobromic or hydriodic acid is, however, an important way of cleaving esters.

c) *Anhydride.* Higher acyl chlorides react slowly with acids when heated to 100° or higher.

$$\underset{\text{butyryl chloride}}{CH_3CH_2CH_2-CO-Cl} + \underset{\text{butyric acid}}{HO-OC-CH_2CH_2CH_3} \longrightarrow \underset{\text{butyric anhydride}}{(CH_3CH_2CH_2-CO)_2O} + HCl$$

d) *Acyl halide.* This is formed from an acid by the action of a large number of inorganic acid halides. Especially useful are phosphorus trichloride, phosphorus pentachloride, and thionyl chloride (see p. 175). Sulfur monochloride and sulfuryl chloride are used in industry. Thionyl chloride is not satisfactory for low boiling acid chlorides, because of loss of product in the stream of gaseous products, but it is one of the best reagents for higher acyl chlorides. Acyl chlorides are much more important than bromides and iodides, owing to greater ease of preparation and lower cost. They are sufficiently reactive.

3. *Reaction of a metallic salt of the* OH *compound with a halogen compound.* These reactions are more rapid and more exothermic than those under (2) above. With an especially reactive halogen compound (organic or inorganic acid halide), the reaction may be violent because it is strongly exothermic.

a) *Ether.*

$$C_2H_5-\bar{O} + I-C_2H_5 \longrightarrow C_2H_5-O-C_2H_5 + I^-$$

This is known as the Williamson synthesis (p. 221), and is especially useful for the preparation of unsymmetrical ethers.

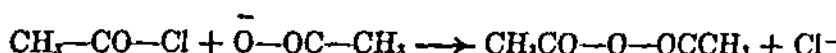
$$CH_3-\bar{O} + I-C_2H_5 \longrightarrow \underset{\text{methyl ethyl ether}}{CH_3-O-C_2H_5} + I^-$$

b) *Ester.*

$$CH_3-CO\bar{O} + I-C_2H_5 \longrightarrow CH_3CO-O-C_2H_5 + I^-$$
$$CH_3-COO-Ag + I-C_2H_5 \longrightarrow CH_3CO-O-C_2H_5 + AgI$$
$$CH_3-CO-Cl + \bar{O}-C_2H_5 \longrightarrow CH_3CO-O-C_2H_5 + Cl^-$$

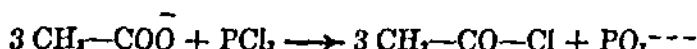
The slowest reaction is the one with the sodium salt of the acid, the fastest with the acyl halide. Silver salts sometimes are used when the acid is rare or expensive.

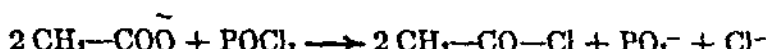
c) Anhydride.



This is a convenient method of preparation.

d) Acid chloride.





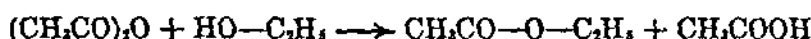
A number of inorganic halides may be used. This method has an advantage over the one starting with the acid, in that side reactions leading to the formation of mixed anhydrides are minimized. If too much of the sodium salt is taken, then reaction under (c) will take place, and an anhydride will result.



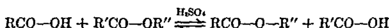
4. *Reaction of an* OH *compound with an anhydride.* The tendency is for a stronger acid to displace a weaker acid from the anhydride, which is considered to include esters and ethers as well as anhydrides and acyl halides.

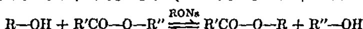
a) Ether. Some cases are known where an alcohol reacts with an ether (p. 214).

b) Ester. One of the most convenient methods of esterifying an alcohol is the reaction with an acid anhydride.

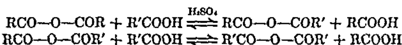


Ester interchange, which involves the reaction of an ester with an acid or an alcohol, sometimes is used as a method of preparation (pp. 215, 217).





c) Anhydride. Anhydride interchange involves the reaction of an acid anhydride with an acid (p. 218).



d) Acyl chloride. Interchange is also possible here (p. 218).

5. *Special methods.* The one deserving particular mention is the formation of methyl esters by the reaction of diazomethane with acids.



This is especially useful with so-called hindered acids, that is, those having substituents at the *alpha*-position.

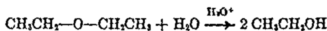
Reactions. Ethers, esters, anhydrides, and acyl halides are first compared in regard to a number of typical reactions, such as hydrolysis, alcoholysis, and ammonolysis, in which a carbon-to-carbon bond is cleaved. The topic of

esterification is then treated in some detail before individual compounds are described.

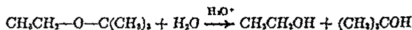
1. *Hydrolysis.*

a) *Ethers.* These are essentially unreactive with water at room temperature. It has been estimated that the period of half hydrolysis of ethyl ether at 25° is 20 million years in neutral solution and 2 years in 1 *N* strong acid. The rate therefore is markedly accelerated by hydronium ions and also of course by a rise in temperature. At 98° the rate is 150 times that at 25°. Hydroxide ions have little effect on the rate of hydrolysis.

The hydrolysis of an ether is the reverse of its formation from the alcohol. Although the equilibrium conditions favor ether formation (p. 145), the hydrolysis reaction can be promoted by a large excess of water. Ethyl *tert*-butyl ether undergoes hydrolysis much more rapidly than diethyl ether.



$$CH_3CH_2—O—CH_2CH_3 + H_2O \xrightarrow{H_3O^+} 2\ CH_3CH_2OH$$



$$CH_3CH_2—O—C(CH_3)_3 + H_2O \xrightarrow{H_3O^+} CH_3CH_2OH + (CH_3)_3COH$$

In general, an unsymmetrical ether having a tertiary alkyl radical undergoes hydrolysis relatively easily.

b) *Esters.* These react slowly with water. The reaction is catalyzed by hydronium or hydroxide ions.

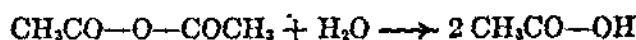


$$CH_3CO—O—C_2H_5 + H_2O \longrightarrow CH_3CO—OH + C_2H_5OH$$

The acid-catalyzed reaction is the reverse of the esterification reaction, which is described in some detail later (pp. 223-226).

A few esters which have a relatively high percentage of oxygen and are somewhat soluble in water, for example, methyl formate, ethyl oxalate, and methyl malonate, undergo hydrolysis rapidly. If attempt is made to neutralize the acid produced by titration with a base to an endpoint, this fades rapidly. Sometimes the ester titrates as an acid.

c) *Anhydrides.* Acetic anhydride reacts slowly with ice-cold water, and within a few minutes with warm water.



$$CH_3CO—O—COCH_3 + H_2O \longrightarrow 2\ CH_3CO—OH$$

Higher anhydrides are less reactive, owing in part to the higher molecular weight, and in part to a lessened solubility in water.

d) *Acid chlorides.* Acetyl chloride reacts vigorously with water.



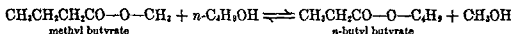
$$CH_3CO—Cl + H_2O \longrightarrow CH_3CO—OH + HCl$$

2. *Alcoholysis.*

a) *Ethers.* Alcoholysis of ethers has been observed. In the presence of anhydrous aluminum chloride, a powerful catalyst, ethyl alcohol and dibutyl ether react to form ethyl butyl ether.

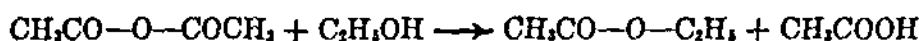
b) *Esters.* Alcoholysis of an ester often is called ester interchange, and takes place slowly when the reactants are heated with a catalyst, which may

be a strong acid, for example, sulfuric acid, or a very strong base, for example, a sodium alkoxide.

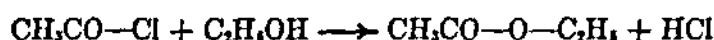


For any such system ΔH and ΔF are quite small, and therefore an equilibrium exists. The position of equilibrium is not altered significantly by a change in temperature. The reaction may be driven to completion if one of the components can be removed from the reaction mixture. This is possible when one of the components is more volatile than the others.

c) *Anhydrides.* Acetic anhydride and alcohol react only slowly at room temperature. Addition of a base or a strong acid accelerates the rate. The base should be one which does not react significantly with the anhydride (see Relative Reactivities, p. 220).



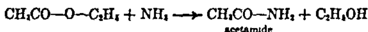
d) *Acid chlorides.* The lower members react vigorously, sometimes violently, with alcohols. Hydrogen chloride is evolved copiously.



3. *Ammonolysis.* Esters, anhydrides, and acyl halides usually undergo ammonolysis more rapidly than hydrolysis or alcoholysis.

a) *Ethers.* There is no apparent change when ether and concentrated aqueous ammonia stand at room temperature.

b) *Esters.* Ethyl acetate and concentrated aqueous ammonia react slowly at room temperature, and within less than a day a one-phase system results from the original two-phase system, owing to the fact that the products, acetamide and ethyl alcohol, are very soluble in water.

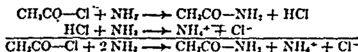


Although higher esters react more slowly, the rate is especially retarded by branching at the *alpha*-position of the acid. The reaction is reversible but the equilibrium lies well to the right. The addition of an anhydrous strong acid to a mixture of acetamide and ethyl alcohol causes a reversal of the reaction.

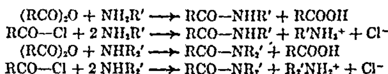
c) *Anhydrides.* These react rapidly with ammonia. Even in aqueous ammonia the main reaction is ammonolysis, to yield an amide.



d) *Acid halides.* These react very rapidly with ammonia, sometimes explosively. Only half of the ammonia is converted to the amide, even with an excess of acyl halide. This is due to the fact that an ammonium halide is relatively inert.



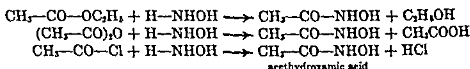
4. *Reaction with amines (primary, RNH_2 and secondary R_2NH); aminolysis.* These substituted ammonias react like ammonia with esters, anhydrides, and acyl halides, and often react more rapidly than does ammonia, because of better solubility relationships. The products are substituted amides of the general formulas, RCONHR′ and $RCONR_2'$. Many of these compounds are solids, and thus are useful in the identification both of acids and of amines.



$$(RCO)_2O + NH_2R' \longrightarrow RCO{-}NHR' + RCOOH$$
$$RCO{-}Cl + 2\,NH_2R' \longrightarrow RCO{-}NHR' + R'NH_3^+ + Cl^-$$
$$(RCO)_2O + NHR_2' \longrightarrow RCO{-}NR_2' + RCOOH$$
$$RCO{-}Cl + 2\,NHR_2' \longrightarrow RCO{-}NR_2' + R_2'NH_2^+ + Cl^-$$

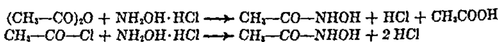
Tertiary amines, R_3N, form addition compounds, often solid, with acyl halides. On the addition of water these are decomposed, and the tertiary amine is recoverable unchanged or in the form of a salt, in case the acyl halide had undergone hydrolysis.

5. *Reaction with hydroxylamine.* Hydroxyamic acids are formed when hydroxylamine in alcoholic solution is heated with esters, acid anhydrides, or acyl halides.



$$CH_3{-}CO{-}OC_2H_5 + H{-}NHOH \longrightarrow CH_3{-}CO{-}NHOH + C_2H_5OH$$
$$(CH_3{-}CO)_2O + H{-}NHOH \longrightarrow CH_3{-}CO{-}NHOH + CH_3COOH$$
$$CH_3{-}CO{-}Cl + H{-}NHOH \longrightarrow \underset{\text{acethydroxamic acid}}{CH_3{-}CO{-}NHOH} + HCl$$

Hydroxylamine hydrochloride reacts with anhydrides or acyl halides but not with esters.



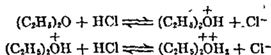
$$(CH_3{-}CO)_2O + NH_2OH{\cdot}HCl \longrightarrow CH_3{-}CO{-}NHOH + HCl + CH_3COOH$$
$$CH_3{-}CO{-}Cl + NH_2OH{\cdot}HCl \longrightarrow CH_3{-}CO{-}NHOH + 2\,HCl$$

The reaction is useful in the detection of these three classes of compounds, for hydroxamic acids give deeply colored red (sometimes violet) ferric salts on the addition of ferric chloride (see Chap. 22).

6. *Reaction with strong acids; the onium reaction.* Strong acids form onium compounds rapidly, because a proton of the acid migrates to an unshared electron pair of an oxygen atom of the organic compound (p. 142). The reaction is essentially the ionization of the acid in the organic solvent, which has weakly basic properties. The ready solubility of an ether or ester in concentrated sulfuric acid is due in part to the formation of the onium compound.

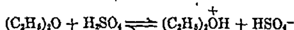
The tendency of such a reaction to take place is a measure of the base strength of the compound. In general, acyl halides are less basic than esters and ethers. The upper limit of the basic constant of ethyl ether is 3×10^{-15}.

a) Ethers. The freezing point curve of ethyl ether with anhydrous hydrogen chloride has two maxima. The positions of these maxima correspond to compositions of products formed according to the following equations.



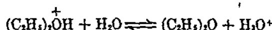
$$(C_2H_5)_2O + HCl \rightleftharpoons (C_2H_5)_2\overset{+}{O}H + Cl^-$$
$$(C_2H_5)_2\overset{+}{O}H + HCl \rightleftharpoons (C_2H_5)_2\overset{++}{O}H_2 + Cl^-$$

Sulfuric acid presumably forms an acid sulfate.



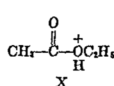
$$(C_2H_5)_2O + H_2SO_4 \rightleftharpoons (C_2H_5)_2\overset{+}{O}H + HSO_4^-$$

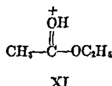
Addition of water decomposes the complex cation, because of the basic properties of water.

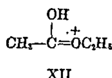


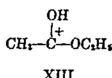
$$(C_2H_5)_2\overset{+}{O}H + H_2O \rightleftharpoons (C_2H_5)_2O + H_3O^+$$

b) Esters. Either oxygen atom could take on the proton. The structure of the onium complex in the case of ethyl acetate could be X or XI.









X XI XII XIII

The latter is of greater interest, for it is regarded as the intermediate which is involved in the acid-catalyzed hydrolysis of esters. It, like acetic acid, is stabilized by resonance. The other electronic forms that contribute to the structure of this complex are shown as XII and XIII. Thus the positive charge may resonate among the two oxygen atoms and the carbon atom. Structure XIII is a less stable form, since the carbon atom does not have a complete octet. However, its contribution to the overall structure is important in connection with chemical reactivity, for it would promote reaction with nucleophilic reagents (see Mechanism of Esterification, p. 225).

c) Anhydrides and acyl halides. These can form oxonium complexes also. They probably are important in the acid-catalyzed reactions of these compounds.

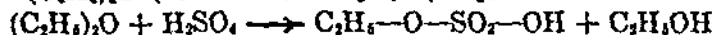
7. *Scission by acids.* In general, these compounds undergo scission when heated with an excess of strong acid.



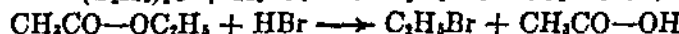
$$(C_2H_5)_2O + HI \longrightarrow C_2H_5I + C_2H_5OH$$



$$(C_2H_5)_2O + 2\,HI \longrightarrow 2\,C_2H_5I + H_2O$$



$$(C_2H_5)_2O + H_2SO_4 \longrightarrow C_2H_5{-}O{-}SO_2{-}OH + C_2H_5OH$$

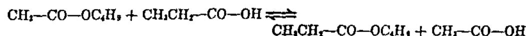


$$CH_3CO{-}OC_2H_5 + HBr \longrightarrow C_2H_5Br + CH_3CO{-}OH$$

For cleaving ethers and esters, often concentrated aqueous hydriodic acid, sometimes hydrogen bromide in glacial acetic acid is used.

Carboxylic acids also may react. The most important reactions are those with esters and anhydrides.

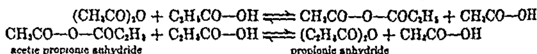
a) Esters. When an ester is heated with a carboxylic acid in the presence of a small amount of concentrated sulfuric acid, which acts catalytically, ester interchange takes place.



$$CH_3{-}CO{-}OC_4H_9 + CH_3CH_2{-}CO{-}OH \rightleftharpoons CH_3CH_2{-}CO{-}OC_4H_9 + CH_3{-}CO{-}OH$$

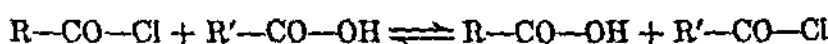
An equilibrium exists, as in the alcoholysis of esters (p. 215). To carry out the reaction the acid to be eliminated must be more volatile than the two esters and the other acid.

b) *Anhydrides.* When an anhydride is heated with a carboxylic acid in the presence of a small amount of an anhydrous strong acid, *e.g.*, hydrogen chloride or sulfuric acid, interchange of acyl radicals takes place.



An equilibrium exists here also. Either the unsymmetrical or the symmetrical anhydride can be prepared by proper proportioning of reactants, and by removing the most volatile compound, in this case acetic acid.

c) *Acyl halides.* Interchange of radicals may take place also between an acid and an acyl halide. The latter should be high boiling in order for the reaction to be of practical value.



When R is phenyl, C_6H_5, a number of aliphatic acid chlorides can be prepared this way.

8. *Reduction.*

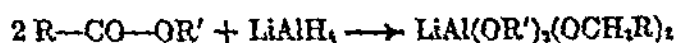
a) *Ethers.* These are not altered. Ether often serves as a solvent when other compounds are being reduced. By working at high temperatures and pressures, ethers can be catalytically cleaved with hydrogen.

b) *Esters.* These are reduced by the action of sodium and an anhydrous alcohol to primary alcohols.

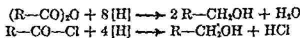


Esters undergo **hydrogenolysis** when heated at 200 to 300° with hydrogen under a pressure of 100 to 300 atmospheres and in the presence of a suitable catalyst, for example, copper chromite, $CuCr_2O_4$. They yield the corresponding primary alcohol (see Hydrogenolysis of Fats, p. 249).

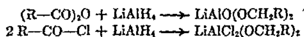
Reduction can be effected also with the much more reactive but much more expensive reducing agent, lithium aluminum hydride.



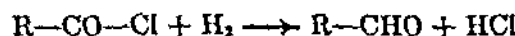
c) *Anhydrides and acid chlorides.* These also are reduced to primary alcohols by metallic sodium. An organic acid, for example, oxalic acid, is added to furnish the hydrogen.



Lithium aluminum hydride reduces both anhydrides and acid chlorides to primary alcohols.



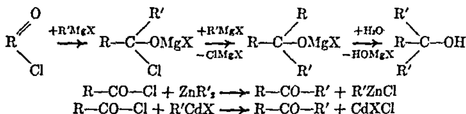
Higher boiling acid chlorides in boiling xylene (temperature about 130°) can be reduced to aldehydes by means of hydrogen in the presence of a poisoned palladium catalyst on barium sulfate (Rosenmund-Kuhn method).



9. *Reaction with organometallic compounds.*

a) Ethers. These do not react. Usually the reaction of organometallic compounds with other compounds is carried out in ether solution. However, epoxy compounds react with Grignard reagents (p. 241).

b) Esters, anhydrides, and acid chlorides. These react with Grignard reagents and with organolithium compounds, yielding alcohols. The reaction of esters is given on page 138. Anhydrides react in analogous fashion. Acid chlorides react with Grignard reagents (2 moles) to yield tertiary alcohols and with dialkylzincs or alkylcadmium halides to yield ketones.



10. *Halogenation.*

a) Ethers. Usually heating is necessary. Substitution takes place at α- and β-carbon atoms first, as in the case of dipropyl ether. Mixtures usually result.

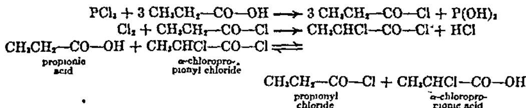


Bromine forms addition compounds with ethers.

b) Esters. The reactions often are complicated. Thus when ethyl acetate is heated with bromine at 150°, the main reaction products are bromoacetic acid, ethyl bromide, and hydrogen bromide.



c) Anhydrides and acid chlorides. These undergo substitution more readily than do the corresponding acids. The role of phosphorus or of a phosphorus halide as a catalyst in chlorination or bromination is believed to involve the formation of the acyl halide, which then undergoes substitution in the *alpha*-position. A small amount of the acyl halide suffices, because an exchange reaction between unchanged acid and halogenated acyl halide regenerates the original acyl halide.



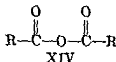
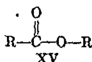
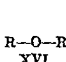
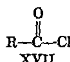
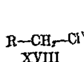
Thus under these conditions propionic acid may undergo mono- or di-substitution in the *alpha*-position (see p. 178).

Relative Reactivities. In hydrolysis, alcoholysis, ammonolysis, or other similar reaction, the relative reactivities usually are in the order below.



$$\text{acyl halides} > \text{anhydrides} > \text{esters} \gg \text{ethers}$$

The carbonyl group, C=O, is seen to have an activating influence on an adjacent carbon-to-oxygen bond. Anhydrides, XIV, contain two carbonyl groups; esters, XV, contain one; and ethers, XVI, none.

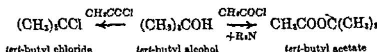
The carbonyl group also has an activating influence on an adjacent carbon-to-halogen bond, for acyl halides, XVII, are much more reactive than alkyl halides, XVIII. The way in which a carbonyl group promotes reaction is described later under Mechanism of Esterification, page 225.

Reactions of esters, anhydrides, and acid chlorides usually are promoted by the presence of bases (refer to Relative Rates of Esterification and Hydrolysis, p. 225). Alcoholysis of anhydrides and acid chlorides often is carried out in the presence of a tertiary amine, R_3N. A primary amine, RNH_2, or a secondary amine, R_2NH, is not satisfactory, since it reacts with the ester, anhydride, or acyl halide.



$$R_3N + CH_3\text{—}CO\text{—}Cl + HOC_2H_5 \longrightarrow CH_3\text{—}CO\text{—}OC_2H_5 + R_3\overset{+}{N}H + Cl^-$$

Moreover tertiary alcohols, which with acyl halides yield tertiary alkyl halides, usually can be converted to esters when a tertiary amine is present.



$$\underset{\textit{tert}\text{-butyl chloride}}{(CH_3)_3CCl} \xleftarrow{CH_3COCl} \underset{\textit{tert}\text{-butyl alcohol}}{(CH_3)_3COH} \xrightarrow[+R_3N]{CH_3COCl} \underset{\textit{tert}\text{-butyl acetate}}{CH_3COOC(CH_3)_3}$$

The accelerating effect of the base upon the typical alcoholysis reaction probably is largely responsible for the different result.

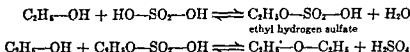
Sometimes the reaction of an acid anhydride or halide is carried out in the presence of an aqueous solution of a strong base in order to increase the rate and to promote completeness of reaction. Usually the acylating reagent is one which reacts only slowly with water under these conditions as, for example, a derivative of a higher acid.

ETHERS

Ethyl Ether, Sulfuric Ether, $(C_2H_5)_2O$. This compound was first obtained about 400 years ago by Valerius Cordus when he distilled a mixture of spirits of wine and oil of vitriol. Up to the time of Williamson's work on ether in 1851 it was supposed that alcohol was a hydrate of ether and that ether was formed from the alcohol by the loss of one molecule of water from one molecule of alcohol. At that time chemists used the equivalent weights of the elements, and since oxygen was 8, wrote the following formulas: water, OH; alcohol, $C_4H_5O \cdot OH$; ether, C_4H_5O.

But when Williamson obtained ether by the action of ethyl iodide upon sodium ethoxide, $C_2H_5O \cdot ONa$ (old formula), he showed that the ether molecule must contain two ethyl radicals and that ether cannot be produced by taking a molecule of water away from one molecule of alcohol. And when he obtained methyl ethyl ether by two different reactions, *i.e.*, methyl iodide on sodium ethoxide and ethyl iodide on sodium methoxide, he showed that the mixed ether must have the structure $CH_3OC_2H_5$ and not $CH_3O \cdot OC_2H_5$. If it had the latter structure, it would be unstable and drop apart into dimethyl and diethyl ethers, just as the hydrated oxides drop apart into the oxide and water. He therefore drew the important conclusions that the atomic weight of oxygen is 16 and that the formulas of water, alcohol, and ether are H—O—H, C_2H_5—O—H, and C_2H_5—O—C_2H_5 respectively.

Ethyl ether is prepared by the "continuous process." Approximately equimolar amounts of alcohol and concentrated sulfuric acid are heated to 130 to 140°. The reaction in the past has been postulated as proceeding in steps, through ethyl hydrogen sulfate (ethyl sulfuric acid), because this compound, which is formed rapidly when the reactants are heated, reacts slowly with alcohol, forming ether, and regenerating sulfuric acid.



$$C_2H_5\text{—}OH + HO\text{—}SO_2\text{—}OH \rightleftharpoons \underset{\text{ethyl hydrogen sulfate}}{C_2H_5O\text{—}SO_2\text{—}OH} + H_2O$$

$$C_2H_5\text{—}OH + C_2H_5O\text{—}SO_2\text{—}OH \rightleftharpoons C_2H_5\text{—}O\text{—}C_2H_5 + H_2SO_4$$

The overall reaction, therefore, is the formation of one mole each of ether and water from two of alcohol (see Ether Formation p. 144).



$$2\,C_2H_5\text{—}OH \rightleftharpoons C_2H_5\text{—}O\text{—}C_2H_5 + H_2O$$

Ether distils as formed, because of its greater volatility. This disturbs the equilibrium, and allows more ether to be formed. More alcohol is allowed to flow in slowly, and the reaction continues. The reaction does not continue indefinitely, however, because in time accumulation of water prevents the formation of ether. Also, some of the acid may be reduced to sulfur dioxide. A given weight of acid allows the formation of 5 to 10 times its weight of ether.

The crude ether is freed of any sulfur dioxide by shaking with aqueous base, and is distilled in order to separate it from most of the alcohol and water. This is the **sulfuric ether** of commerce. **Absolute ether** is ether essentially free of water and alcohol. These often are removed by adding metallic sodium, preferably in wire form, and distilling after the sodium has reacted with the alcohol and water.

Properties and Uses of Ether. Ether boils at 34.5°, is moderately soluble in water (7.3 g. at 20° and 5 g. at 30°), and mixes in all proportions with the concentrated acids such as sulfuric and hydrochloric, also with alcohol and liquid hydrocarbons. It is a good solvent for many organic compounds. Water is slightly soluble in ether (about 2 g. in 100 ml.).

Ether is used as an anesthetic, as a solvent, and when mixed with gasoline, as a motor fuel. It was first used as an anesthetic in 1842 and now finds extensive applications in hospitals for that purpose although within recent years it has to a considerable extent been supplanted by other substances, for example, ethylene, divinyl ether, and cyclopropane, for these have less injurious aftereffects, especially on the lungs.

and alcohol. Since mixtures of ether vapor and air are highly explosive, great care must be exercised when working with ether.

Ether slowly absorbs oxygen from the air and forms an unstable peroxide, the structure of which probably is $C_2H_5O{-}CH(CH_3)O{-}O{-}H$. When ether is evaporated, this peroxide is left behind. The residue has been known to decompose with explosive violence and cause injury.

Isopropyl Ether, $(CH_3)_2CHOCH(CH_3)_2$. This is prepared by heating a mixture of isopropyl alcohol and sulfuric acid (70% acid, 30% water) at 100 to 125°. Some propylene is formed at the same time. If less water is present or if a higher temperature is used, the production of propylene is favored at the expense of the ether. This ether is slightly soluble in water (about 2.7 g. per 100) and dissolves a smaller amount of water than ethyl ether does. As a solvent for oils and waxes it is much like ethyl ether except somewhat better. It dissolves many resins, synthetic as well as natural, but does not dissolve vinylite resins. Because of its lower vapor pressure, isopropyl ether is less subject to fire hazards than ethyl ether and therefore is much safer to use. However, formation of peroxide takes place more extensively than in the case of ethyl ether.

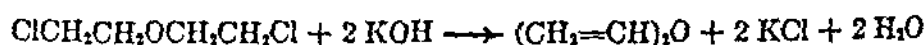
Vinyl Ether, $CH_2{=}CHOCH{=}CH_2$. This is an unsaturated ether. It is prepared by heating β,β'-dichlorodiethyl ether with solid potassium hydroxide.

$$ClCH_2CH_2OCH_2CH_2Cl + 2\,KOH \longrightarrow (CH_2{=}CH)_2O + 2\,KCl + 2\,H_2O$$

This ether is claimed to be much superior to ethyl ether as a general anesthetic.

Other Ethers. Di-*n*-butyl ether sometimes is used as a solvent for Grignard reactions. Dimethyl ether and methyl *tert*-butyl ether differ from most ethers in not forming peroxides. Some physical constants of a number of alkyl ethers are listed in Table 50. Some ethers derived from ethylene glycol are listed in Table 54.

TABLE 50 | **Boiling Points of Some Ethers**



Ether	B.p.	Ether	B.p.
SYMMETRICAL ETHERS			
Methyl ether	−23.6° C	Isobutyl ether	122.5° C
Ethyl ether	34.5	*n*-Amyl ether	190
n-Propyl ether	91	Isoamyl ether	173
Isopropyl ether	69	Vinyl ether	28.3
n-Butyl ether	142.4	Allyl ether	94
UNSYMMETRICAL ETHERS			
Methyl ethyl	10.8° C	Ethyl *n*-propyl	63.6° C
Methyl *n*-propyl	39	Ethyl isopropyl	54
Methyl isopropyl	32	Ethyl *n*-butyl	92.3
Methyl *n*-butyl	71	Ethyl isobutyl	81.1
Methyl isobutyl	59	Ethyl *sec*-butyl	81.2
Methyl *tert*-butyl	54	Ethyl *tert*-butyl	73.1
Methyl *n*-amyl	100	Ethyl *n*-amyl	120

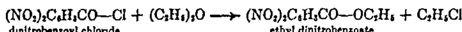
Identification of Ethers. Ethers are so inert chemically that but few characteristic tests are known. They are soluble in cold concentrated sulfuric

acid and are precipitated unchanged on dilution with water. When distilled with concentrated hydriodic acid, they are converted into alkyl iodides which may be identified. From a mixed aliphatic ether two iodides are formed.



$$CH_3OC_2H_5 + 2\,HI \longrightarrow CH_3I + C_2H_5I + H_2O$$

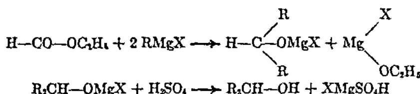
When heated with the acid chloride of dinitrobenzoic acid in the presence of anhydrous zinc chloride, ethers are converted into solid esters which may be readily identified.



$$\underset{\text{dinitrobenzoyl chloride}}{(NO_2)_2C_6H_3CO{-}Cl} + (C_2H_5)_2O \longrightarrow \underset{\text{ethyl dinitrobenzoate}}{(NO_2)_2C_6H_3CO{-}OC_2H_5} + C_2H_5Cl$$

ESTERS

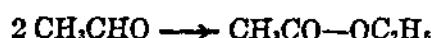
Ethyl Formate, $HCOOC_2H_5$. This is readily prepared by distilling a mixture of sodium formate, ethyl alcohol, and sulfuric acid in approximately equimolal amounts. It boils at 54.3°. It deserves mention because it gives secondary alcohols with Grignard reagents, whereas esters of other acids give tertiary alcohols.



$$H{-}CO{-}OC_2H_5 + 2\,RMgX \longrightarrow H{-}C(R)_2{-}OMgX + Mg(X)(OC_2H_5)$$

$$R_2CH{-}OMgX + H_2SO_4 \longrightarrow R_2CH{-}OH + XMgSO_4H$$

Ethyl Acetate, Acetic Ester (Acetic Ether), $CH_3CO{-}OC_2H_5$. This may be prepared according to the reactions previously given; *viz.*, by heating alcohol and acetic acid with a small amount of a strong acid to catalyze the reaction, by passing a mixture of the two in vapor form over a suitable catalyst such as thorium oxide or titanium dioxide at 150 to 300°, or by adding acetic anhydride or acetyl chloride to alcohol. It is also obtained from aldehyde, CH_3CHO, when it is heated with aluminum ethoxide, $Al(OC_2H_5)_3$ (p. 141).



$$2\,CH_3CHO \longrightarrow CH_3CO{-}OC_2H_5$$

Esterification. When an equimolal mixture of acetic acid and ethyl alcohol stands at room temperature until reaction ceases, only 65 per cent of the acid reacts. On the other hand, if an equimolal mixture of water and ethyl acetate stands for a long time, acid forms gradually. Finally reaction ceases. At this point 33 per cent of the ester and water have been transformed into acetic acid and ethyl alcohol. The reaction is reversible and the final state is essentially the same in the two cases. The position of equilibrium is determined by the relative velocities of the forward and reverse reactions.



$$CH_3CO{-}OH + H{-}OC_2H_5 \rightleftharpoons CH_3CO{-}OC_2H_5 + H_2O$$

According to the mass action law, the velocity v_1, of esterification, *i.e.*, the forward reaction, is proportional to the concentrations of the acid and the

alcohol, and the velocity, v_{-1}, of hydrolysis, *i.e.*, of the reverse reaction, is proportional to the concentrations of the ester and water.

$$v_1 = k_1[\text{acid}][\text{alcohol}]$$
$$v_{-1} = k_{-1}[\text{ester}][\text{water}]$$

Here k_1 and k_{-1} are the velocity constants of the forward and reverse reactions, and the quantities in brackets represent concentrations. At equilibrium the velocities of the opposing reactions are equal, v_1 equals v_{-1} and K, the equilibrium constant, is the ratio of the velocity constants, k_1 and k_{-1}.

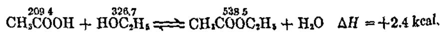
$$k_1[\text{acid}][\text{alcohol}] = k_{-1}[\text{ester}][\text{water}]$$
$$K = \frac{k_1}{k_{-1}} = \frac{[\text{ester}][\text{water}]}{[\text{acid}][\text{alcohol}]}$$

A value of K can be obtained by substituting the actual concentrations for the bracketed terms. If these are expressed in mole fractions then at equilibrium, where two thirds of the initial compounds have reacted, a value of 4 0 is obtained for K, because 0.167 is the mole fraction of each reactant and 0.333 that of each product, when starting with one mole each of acetic acid and ethyl alcohol.

$$K = \frac{[\text{ester}][\text{water}]}{[\text{acid}][\text{alcohol}]} = \frac{(0.333)^2}{(0.167)^2} = 4.0$$

However, the value of K varies over the range, 2.7 to 4.7, as the proportion of acid to alcohol is altered. This variation in the constant results from a change in the nature of the equilibrium mixture and a resultant change in the activity coefficients of the substances involved. The constant is thus not a true thermodynamic equilibrium constant, for which activities, rather than concentrations, must be used. However, the relatively small variation in K shows that the activity coefficients do not change much.

Calculation of ΔH for the liquid phase reaction from heats of combustion gives a value of $+2.4$ kcal.



$$\overset{209.4}{CH_3COOH} + \overset{326.7}{HOC_2H_5} \rightleftharpoons \overset{538.5}{CH_3COOC_2H_5} + H_2O \quad \Delta H = +2.4 \text{ kcal.}$$

For the gas phase reaction at room temperature, if it could take place, ΔH would be $+4$ kcal., calculated from bond energies and resonance energies Taking into account heats of vaporization (5.8, 9.4, 7.7, and 9.7 kcal, respectively), ΔH is $+1.8$ for the liquid phase reaction. This is in good agreement with the value from combustion data. From the small value of ΔH it is reasonable to expect the small value of ΔF which determines the equilibrium system, and the minor effect associated with a change in temperature.

The position of equilibrium in the liquid state is not changed appreciably when the temperature is raised. This is true also of the vapor phase equilibrium which is attained in contact with a suitable catalyst (aluminum oxide): at 75 to 76° the conversion is 88.5 per cent, and at 300°, 88.8 per cent. This indicates that the heat change accompanying esterification in the gas phase is essentially zero.

Relative Rates of Esterification and Hydrolysis. Branching of the carbon chain of the acid retards the rate of esterification. The effect is especially marked in the *alpha*-position. Thus, in the acid-catalyzed reaction of ethyl alcohol with different acids, the relative rates are: acetic acid, 1.0; propionic 0.8; α-methylpropionic (dimethylacetic; isobutyric), 0.5; α,α-dimethylpropionic (trimethylacetic), 0.025; chloroacetic, 0.7; dichloroacetic, 0.02; trichloroacetic, 0.01; tribromoacetic, 0.004.

Branching of the carbon chain of the alcohol retards esterification somewhat. Thus in the case of the butyl alcohols, the relative rates are in the order: *n*-butyl > *sec*-butyl > *tert*-butyl. Actually tertiary alcohols are difficult to esterify because the decomposition of the alcohol to olefin becomes the important reaction.

The accelerating effect of a strong acid on the rate of esterification is proportional to the concentration of this acid, when it is small, and to the relative strength of the acid. The extent to which an acid promotes esterification has been used to measure the strength of the acid, and historically was one of the first important methods applied to this type of investigation.

The equilibrium constant of esterification of any acid by any alcohol is not greatly different from the constant in the ethyl acetate reaction. This indicates that the structural features which affect the acid-catalyzed rate of esterification exert a similar effect upon the reverse acid-catalyzed rate of hydrolysis of the ester.

Hydroxide ion catalyzes the hydrolysis of esters, and this in general is faster than the acid-catalyzed reaction. In the case of methyl formate alkaline hydrolysis is 1300 times as fast as acid hydrolysis. An alkyl substituent at the *alpha*-position in the acid part of the ester retards alkaline hydrolysis similar to the effect on acid hydrolysis, but a negative substituent promotes it. Thus, taking the rate of methyl acetate as unity, methyl chloroacetate is 700, and methyl dichloroacetate is 16,000.

Driving the Reaction to Completion. This can be done by continuous removal of one of the products of the reaction A few low boiling esters, mainly formates, can be distilled from reaction mixtures. Usually, however, it is water which is removed. This is done by distilling over an azeotropic mixture which contains water and an organic liquid in which water is not very soluble. Sometimes this is the ester itself, or in case this is very high boiling, an added volatile liquid such as carbon tetrachloride. Water is separated out and the organic phase is returned to the boiler. The operation is continued until water no longer distils.

Mechanism of Esterification. Esterification differs from neutralization of an acid with a base in two important respects: (1) neutralization is a very fast reaction, esterification is a relatively slow reaction; (2) in neutralization the base furnishes the hydroxyl group, in esterification the acid furnishes it. This last has been established recently by means of heavy oxygen, $\overset{18}{O}$. When methyl alcohol containing $\overset{18}{O}$ reacts with benzoic acid containing oxygen of normal isotopic composition, normal oxygen

is found in the water produced. Thus the oxygen in the water molecule comes from the acid.

$$\underset{\text{benzoic acid}}{C_6H_5\overset{O}{\overset{\|}{C}}{-}\overset{16}{O}{-}H} + H{-}\overset{18}{O}{-}CH_3 \longrightarrow \underset{\text{methyl benzoate}}{C_6H_5\overset{O}{\overset{\|}{C}}{-}\overset{18}{O}{-}CH_3} + H{-}\overset{16}{O}{-}H$$

Evidence that the hydroxyl group is furnished by the acid actually came earlier from a study of esterification reactions involving sulfur compounds.

$$\underset{\text{acetic acid}}{CH_3\overset{O}{\overset{\|}{C}}{-}OH} + \underset{\text{mercaptan}}{H{-}SC_2H_5} \longrightarrow \underset{\text{ethyl thiolacetate}}{CH_3\overset{O}{\overset{\|}{C}}{-}SC_2H_5} + H_2O$$

$$\underset{\textit{thiolacetic acid}}{CH_3\overset{O}{\overset{\|}{C}}{-}SH} + \underset{\text{alcohol}}{H{-}OC_2H_5} \longrightarrow \underset{\text{ethyl acetate}}{CH_3\overset{O}{\overset{\|}{C}}{-}OC_2H_5} + H_2S$$

Thus the idea that the alcohol, in reactions with organic acids, furnishes the hydroxyl group has no foundation experimentally.

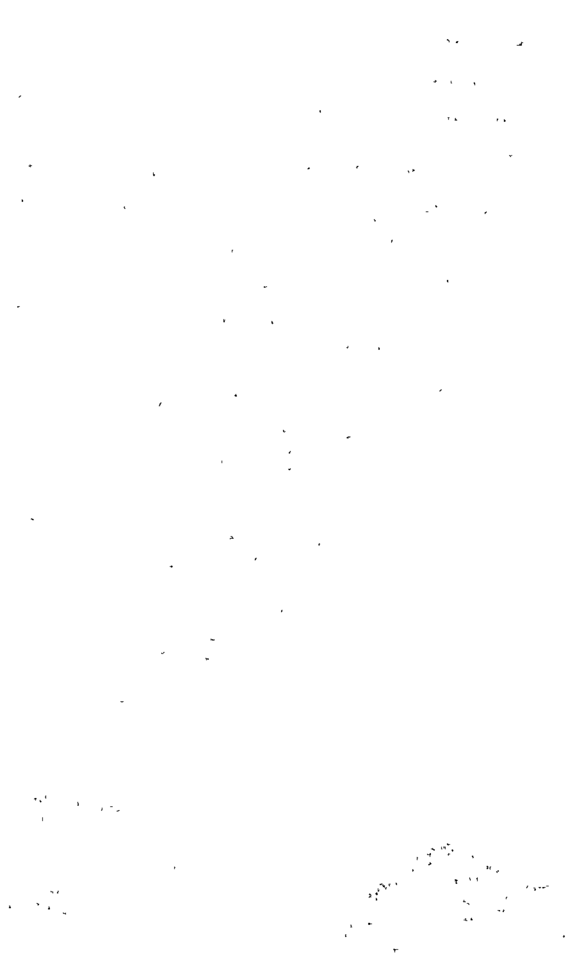
The following steps in the esterification process account in a *satisfactory* manner for the observed phenomena.

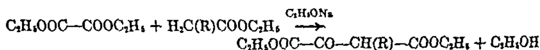
$$CH_3\overset{O}{\overset{\|}{C}}{-}OH \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} \underset{\text{XIX}}{CH_3{-}\overset{\overset{+}{O}H}{\overset{\|}{C}}{-}OH} \underset{-HOC_2H_5}{\overset{+HOC_2H_5}{\rightleftharpoons}} \underset{\text{XX}}{\left[\begin{array}{c} OH \\ | \\ CH_3{-}C{-}OH \\ | \\ H{-}O^+{-}C_2H_5 \end{array}\right]} \rightleftharpoons$$

$$\underset{\text{XXI}}{\left[\begin{array}{c} OH \\ | \\ CH_3{-}C{-}\overset{+}{O}H_2 \\ | \\ OC_2H_5 \end{array}\right]} \underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}} \underset{\text{XI}}{CH_3{-}\overset{\overset{+}{O}H}{\overset{\|}{C}}{-}OC_2H_5} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} \underset{\text{ethyl acetate}}{CH_3{-}\overset{O}{\overset{\|}{C}}{-}OC_2H_5}$$

The first step is believed to be the formation of the protonated complex of acetic acid, XIX. Owing to the contribution of the activated form, similar to XIII (p. 217), the onium complex is believed to add a molecule of alcohol by a simple addition reaction in which the carbon nucleus of the complex ion is attacked by an electron pair of the oxygen atom of an alcohol molecule. The unstable addition compound, XX, either can decompose through a reverse reaction, or can change over, by migration of a proton, to an isomeric, unstable complex, XXI. This can decompose to yield water and the conjugate acid of the ester (protonated ester), XI (p. 217). This decomposition is believed to be promoted by the formal positive charge of the oxygen atom of XXI, for this increases the dipole moment of the carbon-to-oxygen bond. The protonated ester, XI, by loss of the proton gives the final product, ethyl acetate. The reverse operation of hydrolysis is believed to proceed by a similar mechanism, in the reverse order.

The phenomena accounted for by this mechanism are: (1) the catalytic effect of strong acid on the forward and reverse reactions; (2) the furnishing of the hydroxyl group in esterification by the acid, (3) the retarding of esterification by branching of



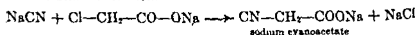


$$C_2H_5OOC{-}COOC_2H_5 + H_2C(R)COOC_2H_5 \xrightarrow{C_2H_5ONa} C_2H_5OOC{-}CO{-}CH(R){-}COOC_2H_5 + C_2H_5OH$$

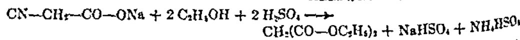
TABLE 51 | **Boiling Points of Some Esters**

ETHYL ESTERS	°C	ACETATES	°C
Formate	54.3	Methyl	57.5
Acetate	77 1	Ethyl	77.1
Propionate	99.1	*n*-Propyl	101.7
n-Butyrate	121 3	*n*-Butyl	126 5
n-Valerate	145 5	*n*-Amyl	148
n-Caproate	166.6	*n*-Hexyl	169.2
n-Heptylate	188.6	*n*-Heptyl	191.5
n-Caprylate	205.8	*n*-Octyl	210.1
UNSATURATED ESTERS			
Methyl acrylate	80 3	Vinyl acetate	72 5
Methyl methacrylate	101	Allyl acetate	104
ESTERS OF DIBASIC ACIDS			
Methyl oxalate	163 3	Ethyl oxalate	186
Methyl malonate	180 1	Ethyl malonate	198 9
Methyl succinate	195.3	Ethyl succinate	216 5
ORTHO ESTERS			
Ethyl orthoformate	146	Ethyl orthoacetate	142

Ethyl Malonate, Malonic Ester, $C_2H_5OOC{-}CH_2{-}COOC_2H_5$. This is prepared from chloroacetic acid through the nitrile synthesis, followed by a combined alcoholysis and esterification reaction.

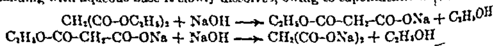


$$NaCN + Cl{-}CH_2{-}CO{-}ONa \longrightarrow \underset{\text{sodium cyanoacetate}}{CN{-}CH_2{-}COONa} + NaCl$$



$$CN{-}CH_2{-}CO{-}ONa + 2\,C_2H_5OH + 2\,H_2SO_4 \longrightarrow CH_2(CO{-}OC_2H_5)_2 + NaHSO_4 + NH_4HSO_4$$

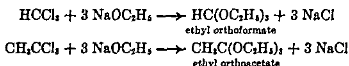
Ethyl malonate is a liquid of pleasant odor. It decomposes some when distilled at atmospheric pressure, b p. 199°. It is only very slightly soluble in water On standing with aqueous base it slowly dissolves, owing to saponification.



$$CH_2(CO\text{-}OC_2H_5)_2 + NaOH \longrightarrow C_2H_5O\text{-}CO\text{-}CH_2\text{-}CO\text{-}ONa + C_2H_5OH$$
$$C_2H_5O\text{-}CO\text{-}CH_2\text{-}CO\text{-}ONa + NaOH \longrightarrow CH_2(CO\text{-}ONa)_2 + C_2H_5OH$$

Malonic ester is the most important dicarboxylate ester. It is useful in the synthesis of alkylated malonic acids and of alkylated acetic acids (p. 331). It reacts readily with urea to form barbituric acid (p. 378).

Esters of Orthoacids. Ethyl orthoformate and ethyl orthoacetate are obtained by the action of sodium ethoxide on chloroform and on 1,1,1-trichloroethane, respectively.

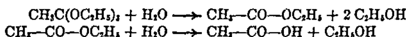


$$HCCl_3 + 3\,NaOC_2H_5 \longrightarrow \underset{\text{ethyl orthoformate}}{HC(OC_2H_5)_3} + 3\,NaCl$$

$$CH_3CCl_3 + 3\,NaOC_2H_5 \longrightarrow \underset{\text{ethyl orthoacetate}}{CH_3C(OC_2H_5)_3} + 3\,NaCl$$

These are stable compounds (b.p. 146° and 142°, respectively), and are esters of the respective hypothetical acids, orthoformic acid, $HC(OH)_3$ and orthoacetic acid, $CH_3C(OH)_3$. The esters are stable towards aqueous base.

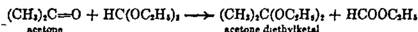
Orthoesters undergo acid hydrolysis, with formation first of the corresponding carboxylate esters, which can hydrolyse to the acid.



$$CH_3C(OC_2H_5)_3 + H_2O \longrightarrow CH_3{-}CO{-}OC_2H_5 + 2\,C_2H_5OH$$

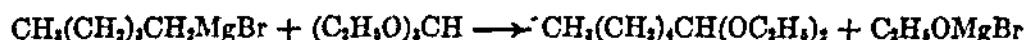
$$CH_3{-}CO{-}OC_2H_5 + H_2O \longrightarrow CH_3{-}CO{-}OH + C_2H_5OH$$

Orthoesters are excellent alkylating agents. They even react with aldehydes and ketones, yielding acetals and ketals, respectively (p. 267). Ketals are difficult to prepare otherwise.



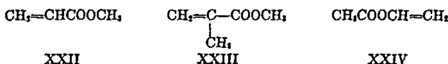
$$\underset{\text{acetone}}{(CH_3)_2C{=}O} + HC(OC_2H_5)_3 \longrightarrow \underset{\text{acetone diethylketal}}{(CH_3)_2C(OC_2H_5)_2} + HCOOC_2H_5$$

Ethyl orthoformate reacts with Grignard reagents, to yield acetals of aldehydes. Thus *n*-amylmagnesium bromide is converted to hexaldehyde acetal.



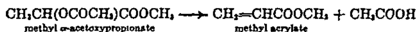
$$CH_3(CH_2)_3CH_2MgBr + (C_2H_5O)_3CH \longrightarrow CH_3(CH_2)_4CH(OC_2H_5)_2 + C_2H_5OMgBr$$

Unsaturated Esters. Some of these are quite important industrially, more especially methyl acrylate, XXII, methyl methacrylate, XXIII, and vinyl acetate, XXIV, as sources of useful synthetic resins.



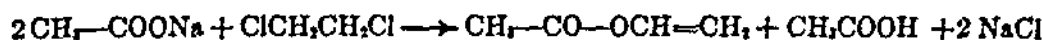
$$\underset{\text{XXII}}{CH_2{=}CHCOOCH_3} \qquad \underset{\text{XXIII}}{CH_2{=}C(CH_3){-}COOCH_3} \qquad \underset{\text{XXIV}}{CH_3COOCH{=}CH_2}$$

Methyl esters of unsaturated acids usually are manufactured by pyrolysis of methyl esters of α-acetoxy acids (acetates of α-hydroxy acids).



$$\underset{\text{methyl }\alpha\text{-acetoxypropionate}}{CH_3CH(OCOCH_3)COOCH_3} \longrightarrow \underset{\text{methyl acrylate}}{CH_2{=}CHCOOCH_3} + CH_3COOH$$

Vinyl acetate is manufactured by heating ethylene chloride with sodium acetate under pressure. This brings about dehydrohalogenation, as well as displacement of one chloro by the aceto group.



$$2\,CH_3{-}COONa + ClCH_2CH_2Cl \longrightarrow CH_3{-}CO{-}OCH{=}CH_2 + CH_3COOH + 2\,NaCl$$

Vinyl acetate may be prepared also by the addition of acetic acid to acetylene. This is carried out industrially in the presence of mercuric sulfate, which acts catalytically.



$$CH_3{-}CO{-}OH + HC{\equiv}CH \longrightarrow CH_3{-}CO{-}OCH{=}CH_2$$

Synthetic Resins from Unsaturated Esters. One of the best known synthetic resins of this type is Lucite (or Plexiglas) a transparent, glasslike material obtained by the polymerization of methyl methacrylate (methyl methylacrylate). The polymerization will take place very slowly on exposure to air because of the slow formation of peroxides, and proceeds more rapidly when organic peroxides are added. Benzoyl peroxide has been used extensively for this purpose, but other, less stable peroxides are supplanting it, because with them the polymerization can be effected at a lower temperature. The polymerization is a chain reaction and proceeds by a free radical mechanism induced by the decomposition of the organic peroxide (p. 90).

The manufacture of synthetic resins of the Lucite type received enormous impetus during World War II because of their extensive use in airplanes where visibility is necessary, but where glass cannot be used. These resins are also extensively used for making molded objects. Synthetic resins are much softer than glass and scratch easily, but improved resins with greater hardness are being developed.

Vinyl acetate gives polyvinyl acetate, a useful synthetic resin. Often the acetate is copolymerized with vinyl chloride to give the "vinylite" resins. Many of these have properties resembling rubber and are employed for manufacture of numerous commercial products.

Identification of Esters. A few esters are solids and may be identified by their melting points. Although the boiling point is useful, it cannot be used as a means of identification because several esters may boil within a few degrees of each other. An aid in the identification is the determination of the saponification equivalent.

In general an ester must be converted into the constituent acid and alcohol and these identified separately. The ester is saponified by refluxing with an aqueous solution of a base, and when the reaction is finished, the alcohol is distilled over and identified. Evaporation of the solution leaves the salt of the acid, which may be identified by the usual methods. A slightly volatile alcohol such as glycol is extracted from the salt by means of a suitable organic solvent.

Many esters evolve hydrogen on the addition of metallic sodium with the formation of esters of higher molecular weight. Because of this fact the evolution of hydrogen cannot be used as a distinguishing test for hydroxyl hydrogen.

Esters may be detected conveniently by means of the ferric hydroxamate test (p. 375). This test is given also by anhydrides, acyl halides, and amides.

ESTERS OF INORGANIC ACIDS

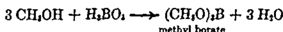
The distinguishing feature of an ester is the fact that it is formed by the reaction of an alcohol with an acid. Thus, even though the acid is inorganic, the product is an ester. Although there is a formal resemblance, structurally, between an inorganic acid such as nitric acid, a salt of the acid, and an ester of the acid, an ester differs markedly from a salt in three respects: (1) it is a liquid, or a solid of relatively low melt-

ing point; (2) it is insoluble (or slightly soluble) in water; (3) it is not ionized. Thus the older name for an ester, *viz.*, "ethereal salt," is misleading.

An ester of an inorganic acid can be prepared by one or more of the following reactions: (1) an alcohol with an inorganic acid chloride; (2) an alcohol with an inorganic acid; (3) an alcohol with an inorganic anhydride; (4) a carboxylic ester with an inorganic acid. The first method is general. The other methods often fail when the inorganic acid is weak.

Alkyl Halides. These may be regarded as esters of the hydrogen halides. They differ from almost all other esters in not containing oxygen, and on that account do not dissolve in concentrated sulfuric acid. These compounds are described in Chapter 8.

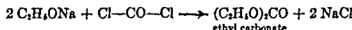
Alkyl Borates. Boric acid reacts with alcohols to form the trialkyl borates. Sometimes sulfuric acid is added to act as a catalyst.



$$3\,CH_3OH + H_3BO_3 \longrightarrow \underset{\text{methyl borate}}{(CH_3O)_3B} + 3\,H_2O$$

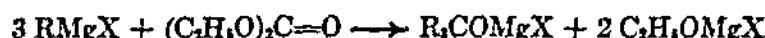
Organic borates hydrolyze rapidly. For storage they must be kept in airtight containers. They burn with a green flame. This forms the basis of a qualitative test for boric acid or a salt.

Alkyl Carbonates. These are prepared by the action of phosgene on alcohols or on sodium alkoxides.



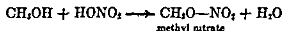
$$2\,C_2H_5ONa + Cl{-}CO{-}Cl \longrightarrow \underset{\text{ethyl carbonate}}{(C_2H_5O)_2CO} + 2\,NaCl$$

They yield tertiary alcohols with Grignard reagents.



$$3\,RMgX + (C_2H_5O)_2C{=}O \longrightarrow R_3COMgX + 2\,C_2H_5OMgX$$

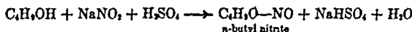
Alkyl Nitrates. These usually are prepared from the alcohols with a mixture of anhydrous (fuming) nitric acid and sulfuric acid, under carefully controlled conditions.



$$CH_3OH + HONO_2 \longrightarrow \underset{\text{methyl nitrate}}{CH_3O{-}NO_2} + H_2O$$

These esters are unstable, and sometimes, especially when in contact with nitric acid, decompose violently.

Alkyl Nitrites. Alcohols react rapidly in dilute aqueous solution with nitrous acid (from sodium nitrite and sulfuric acid, or from other similar compounds).



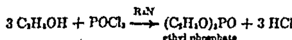
$$C_4H_9OH + NaNO_2 + H_2SO_4 \longrightarrow \underset{n\text{-butyl nitrite}}{C_4H_9O{-}NO} + NaHSO_4 + H_2O$$

Organic nitrites often react with organic compounds in the same way nitrous acid does, and have the advantage that the reaction can be carried out in the absence of water. A typical reaction is the one with methyl ethyl ketone, to form nitroso methyl ethyl ketone (biacetylmonoxime).



$$CH_3{-}CO{-}CH_2CH_3 + C_4H_9O{-}NO \longrightarrow CH_3{-}CO{-}CH(NO)CH_3 + C_4H_9OH$$

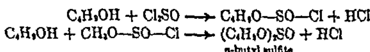
Alkyl Phosphates. These are prepared by the reaction of the corresponding alcohol and phosphorus oxychloride in the presence of a suitable tertiary amine (pyridine).



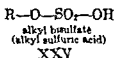
$$3\,C_2H_5OH + POCl_3 \xrightarrow{R_3N} \underset{\text{ethyl phosphate}}{(C_2H_5O)_3PO} + 3\,HCl$$

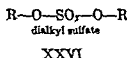
Alkyl Silicates. These are described in Chapter 25.

Alkyl Sulfites. These are best obtained by the action of thionyl chloride on alcohols.



Alkyl Sulfates. There are two series of sulfates, *viz.*, the acid sulfates, XXV, and the neutral sulfates, XXVI.



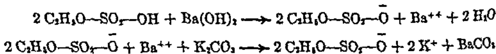


Acid sulfates. A lower alcohol reacts fairly rapidly when heated with concentrated sulfuric acid, to form the acid sulfate. This type of reaction is called sulfation.



The reaction is reversible. The alcohol may be recovered by adding water and distilling.

Ethyl hydrogen sulfate may be isolated as a salt by means of the reactions below.

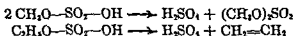


Barium (or calcium) hydroxide precipitates unreacted sulfuric acid as barium (or calcium) sulfate and converts ethyl hydrogen sulfate to the barium (or calcium) salt. Potassium carbonate precipitates barium (or calcium) ion as the carbonate. Evaporation of the solution yields the potassium salt of the half ester reasonably pure, provided the correct amounts of reagents have been added. The ready solubility in water of the barium (or calcium) alkyl sulfates permits removal of sulfate ion. Calcium salts of high molecular weight compounds, up to C_{12}, are soluble.

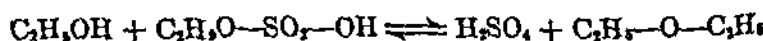
The sulfation reaction may be carried to completion, from the standpoint of sulfuric acid by taking an excess of anhydrous alcohol and removing water. This is easily done by distilling out alcohol along with some of the water.

Industrially alkyl hydrogen sulfates are obtained from olefins and sulfuric acid. Ethylene is so unreactive that a temperature of about 100° is necessary. However, in the presence of cuprous or silver salts reaction proceeds at a lower temperature.

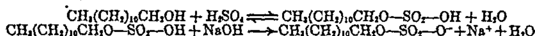
The alkyl hydrogen sulfates are strong acids. When heated to about 150° they decompose to yield sulfuric acid and an olefin. However, the methyl compound yields dimethyl sulfate at 200°.



When ethyl hydrogen sulfate is heated with ethyl alcohol, ethyl ether is formed. This reaction has been postulated as one of the steps in the preparation of ethyl ether by the continuous process (p. 221).

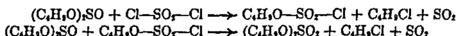


Higher alkyl hydrogen sulfates, C_8 to C_{18}, form sodium salts which, like soaps, lower the surface tension of water and therefore are detergents. One of the best known is sodium lauryl sulfate.



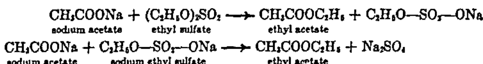
Lauryl alcohol is obtained by the hydrogenolysis of fats containing much laurin (p. 249). Sodium lauryl sulfate has been marketed under various trade names (Dreft, Dreen, etc.). It can be used in hard water without the formation of a precipitate, since calcium lauryl sulfate is somewhat soluble in water.

Dialkyl sulfates. The methyl ester may be obtained by heating methyl hydrogen sulfate. The methyl and ethyl esters are manufactured by rapidly passing the vapor of sulfuric acid, mixed with the vapor of the corresponding alcohol, through reaction zones at temperatures above 300°. Ethyl sulfate is formed to some extent when ethylene is passed into concentrated sulfuric acid. Increase in pressure of ethylene favors diethyl sulfate. A convenient laboratory method, especially useful for higher sulfates, involves heating the corresponding sulfite with sulfuryl chloride.



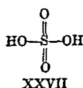
This is a useful general method, for reactants and other products are much more volatile than the sulfate, which can be obtained reasonably pure. However, since they are liable to decompose when distilled at atmospheric pressure, distillation at reduced pressure is customary.

The potassium alkyl sulfates and the dialkyl sulfates are useful alkylating agents, excelling alkyl halides for many purposes. They react with metallic alkoxides, RONa, to form ethers, with salts of organic acids to form esters, with potassium cyanide to form nitriles, with alkali sulfides and bisulfides to form organic sulfides and mercaptans respectively, with sodium malonic ester to form alkylated malonic esters, with salts of other compounds (phenols, for example), and with primary and secondary amines.

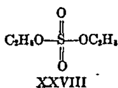


A higher temperature is required for the second reaction, for the first ethyl group of ethyl sulfate sometimes is replaced thousands of times more easily than the second. Great caution must be taken when using dimethyl sulfate, the vapors of which, even in low concentration, are toxic. The eyes and throat are especially susceptible and may suffer severe damage.

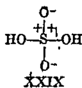
Structures. On the basis of the older classical valence theory, according to which sulfur has a polar number of six, sulfuric acid is represented as XXVII and ethyl sulfate as XXVIII. On the assumption that the sulfur atom has a complete octet of electrons, and no more, in its valence shell, sulfuric acid is XXIX, and ethyl sulfate is XXX.



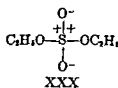
XXVII



XXVIII



XXIX



XXX

It is believed now that the structures are not as simple as those shown by XXIX and XXX, but that actually there is resonance involving forms in which a double bond exists between the sulfur and one or more oxygen atoms. Thus a sulfur-to-oxygen bond probably is a combination of a single and a double bond. In order for a double bond to form, the sulfur atom must expand its octet to ten electrons.

TABLE 52 | Some Esters of Inorganic Acids

NAME	FORMULA	B.P. °C	NAME	FORMULA	B.P. °C
Methyl borate	$(CH_3O)_3B$	72	n-Butyl nitrite	C_4H_9ONO	77–79
Ethyl borate	$(C_2H_5O)_3B$	120	Isoamyl nitrite	$C_5H_{11}ONO$	99
Methyl carbonate	$(CH_3O)_2CO$	90–91	Methyl phosphate	$(CH_3O)_3PO$	197.2
Ethyl carbonate	$(C_2H_5O)_2CO$	126	Ethyl phosphate	$(C_2H_5O)_3PO$	216
Methyl nitrate	CH_3ONO_2	65	Methyl sulfate	$(CH_3O)_2SO_2$	188.6
Ethyl nitrate	$C_2H_5ONO_2$	87–88	Ethyl sulfate	$(C_2H_5O)_2SO_2$	210.2
Methyl nitrite	CH_3ONO	−12	Methyl sulfite	$(CH_3O)_2SO$	126.5
Ethyl nitrite	C_2H_5ONO	17	Ethyl sulfite	$(C_2H_5O)_2SO$	158

ANHYDRIDES

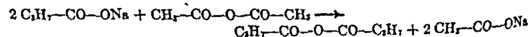
Acetic anhydride, $(CH_3CO)_2O$, is the simplest member of the organic anhydrides. The corresponding derivative of formic acid, $(HCO)_2O$, does not exist. When attempt is made to prepare it, carbon monoxide is formed. Acetic anhydride is the most important member of the series. It is produced on an industrial scale by the reaction of acetic acid with sulfur monochloride, one of the cheapest chlorides of the nonmetals.



$$8\,CH_3COOH + 3\,S_2Cl_2 \longrightarrow 4\,(CH_3CO)_2O + H_2SO_4 + 6\,HCl + 5\,S$$

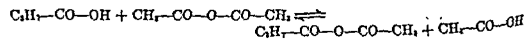
The reactions of acetic anhydride are given on pages 214–219. Acetic anhydride is useful in organic analysis for the detection of the alcoholic hydroxyl group and of primary and secondary amino groups. Commercially it is employed in the production of cellulose acetate.

Higher homologs of acetic anhydride are known. They may be obtained by heating the salts of the acids with acetic anhydride.



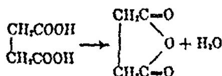
$$2\,C_3H_7{-}CO{-}ONa + CH_3{-}CO{-}O{-}CO{-}CH_3 \longrightarrow C_3H_7{-}CO{-}O{-}CO{-}C_3H_7 + 2\,CH_3{-}CO{-}ONa$$

Mixed anhydrides of acetic acid with the higher acids are obtained by heating these higher acids with acetic anhydride.



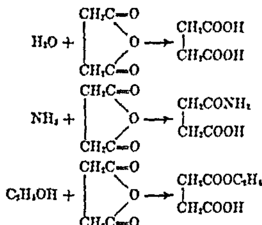
$$C_3H_7{-}CO{-}OH + CH_3{-}CO{-}O{-}CO{-}CH_3 \rightleftharpoons C_3H_7{-}CO{-}O{-}CO{-}CH_3 + CH_3{-}CO{-}OH$$

Anhydrides of Dibasic Acids. When heated above its melting point, succinic, glutaric, or maleic acid is slowly converted (pp. 188, 203) into the respective solid cyclic anhydride. For preparative purposes it is better to heat the acid with acetyl chloride or phosphorus oxychloride.

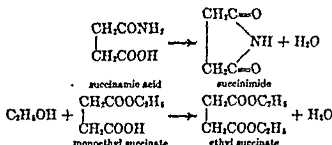


The molecules of succinic and maleic anhydride have a five-membered ring, that of glutaric a six-membered ring.

Each anhydride undergoes hydrolysis to the acid, ammonolysis to a *half amide*, and alcoholysis to a *half ester*, as typified in the case of succinic anhydride, below.



When heated, succinamic acid is converted to succinimide; when heated with an excess of alcohol in the presence of an acid catalyst, ethyl hydrogen succinate is converted to ethyl succinate.



Identification of Anhydrides. Anhydrides give an acid reaction when added to [illegible]

acting with ammonia or amines. However, esters and acid chlorides likewise form amides.

Anhydrides may be detected by the ferric hydroxamate test, involving the use of hydroxylamine hydrochloride. Acyl halides also give the test.

ACID CHLORIDES

Formyl chloride, HCOCl, is not known. When attempt is made to prepare it, carbon monoxide and hydrogen chloride are the products of the reaction. Under certain conditions a mixture of these two gases behaves as if it were formyl chloride. (See the Gatterman synthesis of aromatic aldehydes, Chap. 32.)

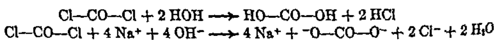
Acetyl chloride, CH_3COCl, is the simplest and at the same time the most important acid chloride. It is a liquid which boils at 50.9°, solidifies at −112°, and fumes in moist air owing to the formation of hydrogen chloride and acetic acid through hydrolysis. It reacts with water, alcohol, ammonia, and substituted ammonias at a very rapid rate. It is a good reagent to use in making esters of acetic acid with alcohols or for preparing substituted amides with ammonia derivatives. Like acetic anhydride it is valuable in testing for the alcoholic hydroxyl group and for the NH_2 and NH groups of primary and secondary amines.

Carbonyl Chloride, Phosgene, $COCl_2$. This is the acid chloride of carbonic acid, $OC(OH)_2$. It cannot be made from the acid since the latter has no existence except in aqueous solution. It is produced when a mixture of carbon monoxide and chlorine is illuminated or when it is passed over activated charcoal.



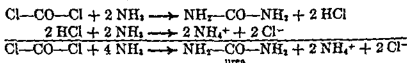
$$CO + Cl_2 \longrightarrow Cl{-}CO{-}Cl$$

Carbonyl chloride is a gas liquefying at 8°. It is very toxic and was one of the first gases used during World War I. Like chlorine it is easily absorbed by a gas mask. Phosgene resembles acetyl chloride in its general chemical behavior. It is hydrolyzed by water to carbonic acid and by a base to a carbonate.



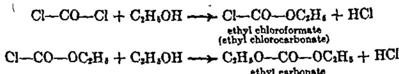
$$Cl{-}CO{-}Cl + 2\,HOH \longrightarrow HO{-}CO{-}OH + 2\,HCl$$
$$Cl{-}CO{-}Cl + 4\,Na^+ + 4\,OH^- \longrightarrow 4\,Na^+ + {}^-O{-}CO{-}O^- + 2\,Cl^- + 2\,H_2O$$

With ammonia phosgene forms urea.



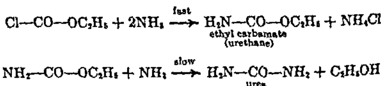
$$Cl{-}CO{-}Cl + 2\,NH_3 \longrightarrow NH_2{-}CO{-}NH_2 + 2\,HCl$$
$$2\,HCl + 2\,NH_3 \longrightarrow 2\,NH_4^+ + 2\,Cl^-$$
$$Cl{-}CO{-}Cl + 4\,NH_3 \longrightarrow \underset{\text{urea}}{NH_2{-}CO{-}NH_2} + 2\,NH_4^+ + 2\,Cl^-$$

Phosgene may react with one or two molecules of alcohol.



$$Cl{-}CO{-}Cl + C_2H_5OH \longrightarrow \underset{\substack{\text{ethyl chloroformate} \\ \text{(ethyl chlorocarbonate)}}}{Cl{-}CO{-}OC_2H_5} + HCl$$
$$Cl{-}CO{-}OC_2H_5 + C_2H_5OH \longrightarrow \underset{\text{ethyl carbonate}}{C_2H_5O{-}CO{-}OC_2H_5} + HCl$$

Ethyl chloroformate is both an ester and an acid chloride and undergoes the typical reactions of each. Ammonia, for example, reacts with each functional group.



$$Cl{-}CO{-}OC_2H_5 + 2NH_3 \xrightarrow{\text{fast}} \underset{\substack{\text{ethyl carbamate} \\ \text{(urethane)}}}{H_2N{-}CO{-}OC_2H_5} + NH_4Cl$$
$$NH_2{-}CO{-}OC_2H_5 + NH_3 \xrightarrow{\text{slow}} \underset{\text{urea}}{H_2N{-}CO{-}NH_2} + C_2H_5OH$$

Identification of Acyl Halides. Acid chlorides are easily distinguished because of their pronounced chemical reactivity. When added to alcohols the evolution of hydrogen chloride is a characteristic phenomenon. Also they give a positive hydroxamic acid test (p. 216) with hydroxylamine hydrochloride. Anhydrides also give the test.

Acyl halides are identified by conversion to solid derivatives through the reaction with ammonia or substituted ammonias. In general, the reactivity of the higher molecular weight chlorides is less than that of the simpler compounds.

TABLE 53 | Some Acid Anhydrides and Acyl Halides

NAME	B.P. °C	NAME	B.P. °C
Acetic anhydride	139.6	*n*-Valeryl chloride	127–128
Propionic anhydride	168 8	Acetyl bromide	76
n-Butyric anhydride	199 5	Propionyl bromide	103–104
n-Valeric anhydride	218	Succinic anhydride [a]	261
Acetyl chloride	51	Glutaric anhydride [b]	150 (10 mm.)
Propionyl chloride	80	Maleic anhydride [c]	202 (subl)
n-Butyryl chloride	101–102		

[a] m.p. 119.6°. [b] m.p. 56°. [c] m.p. 60°

PROBLEMS

1. Write the structure of the product formed by the elimination of one mole of water from two moles of:

a) methyl alcohol
b) isopropyl alcohol
c) 2-butanol
d) 2-pentanol
e) 3-pentanol
f) isobutyl alcohol
g) isoamyl alcohol
h) isohexyl alcohol

2. Write a balanced equation for each of three satisfactory methods for the preparation of the following by the Williamson synthesis; state which method is superior from the standpoint of side reactions and of purification from unreacted material:

a) methyl *n*-propyl ether
b) methyl *n*-butyl ether
c) methyl *n*-amyl ether
d) methyl isopropyl ether
e) methyl *tert*-butyl ether
f) methyl isoamyl ether
g) ethyl *n*-propyl ether
h) ethyl isopropyl ether
i) ethyl *n*-butyl ether
j) ethyl *n*-amyl ether

3. Indicate four methods by which the following may be prepared, without taking any other organic compound:

a) *n*-propyl propionate from *n*-propyl alcohol
b) isobutyl isobutyrate from isobutyl alcohol
c) *n*-amyl *n*-valerate from *n*-amyl alcohol
d) isoamyl isovalerate from isoamyl alcohol
e) *n*-hexyl *n*-hexoate from *n*-hexyl alcohol

4. Starting with *n*-butyl alcohol, and without using any other organic compound, indicate the operations that would be involved in a satisfactory laboratory preparation of the following:

a) *n*-butyl ether
b) *n*-butyryl chloride
c) *n*-butyric anhydride
d) *n*-butyl *n*-butyrate
e) *n*-butyramide
f) *n*-butyl *n*-valerate
g) *n*-amyl *n*-butyrate
h) *n*-valeramide
i) *n*-valeric anhydride
j) *n*-amyl ether
k) 5-*n*-propyl-5-nonanol
l) 5-*n*-butyl-5-nonanol

m) 6-*n*-propyl-6-undecanol
n) 6-*n*-butyl-6-undecanol
o) *n*-butyl orthobutyrate
p) *n*-butyl carbonate
q) *n*-butyl nitrite
r) *n*-butyl phosphate
s) *n*-butyl sulfite
t) *n*-butyl sulfate
u) *n*-butyl ethylmalonate
v) α-bromoethylmalonic acid

5. Starting with methyl propionate as the only organic substance except in (*f*) and not excluding sodium cyanide, indicate the steps involved in obtaining the following:

a) sodium propionate
b) zinc propionate
c) *n*-propyl alcohol
d) methyl bromide
e) propionyl chloride
f) *n*-amyl propionate
g) α-chloropropionic acid
h) methylmalonic acid
i) α-bromomethylmalonic acid
j) 2-methyl-2-butanol
k) 4-ethyl-4-heptanol
l) propionic anhydride
m) *n*-propyl carbonate
n) methyl orthopropionate

6. Write equations for the reactions that *n*-propyl *n*-propionate undergoes when:

a) heated with dilute hydrobromic acid
b) heated with hydrogen bromide in glacial acetic acid
c) heated with aqueous sodium hydroxide
d) heated to about 150° with conc. sulfuric acid
e) allowed to stand with conc ammonium hydroxide
f) distilled with *n*-butyl alcohol containing sodium *n*-propoxide
g) added to ethyl magnesium bromide
h) added to *n*-propyl magnesium bromide

7. Describe a chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) ethyl ether and *n*-pentane
b) *n*-butyl ether and *n*-butyric acid
c) *n*-propyl ether and *n*-propyl acetate
d) *n*-propyl ether and *n*-propyl alcohol
e) *n*-propyl acetate and *n*-propyl alcohol
f) methanol and methyl *n*-butyl ether
g) "isooctane" and *n*-propyl acetate
h) ethyl acetate and acetic acid
i) allyl acetate and *n*-propyl acetate
j) ethyl chloroacetate and carbon tetrachloride
k) allyl acetate and allyl alcohol
l) allyl acetate and allyl ether
m) acetyl chloride and chloroacetic acid
n) acetyl chloride and chloroform
o) acetic anhydride and ethyl acetate
p) acetic anhydride and acetic acid

8. Describe a procedure by which a mixture of the two compounds, approximately equal in amount, can be readily separated so that at least one, preferably both, can be recovered reasonably quantitatively and essentially free of the other. State separation procedure (filtration, distillation, separatory funnel separation, etc.) solvent if any, and any reagent. Note that hydroxy compounds often form azeotropic mixtures when distilled with non-polar liquids.

a) *n*-propyl acetate and acetic acid
b) *n*-propyl propionate and propionic acid
c) *n*-propyl ether and acetic acid

d) *n*-butyl acetate and acetic acid
e) *n*-butyl acetate and *n*-butyl ether
f) *n*-butyl ether and *n*-octane
g) *n*-butyl acetate and acetic anhydride
h) ethyl acetate and carbon tetrachloride
i) *n*-propyl acetate and *n*-heptane
j) *n*-propyl ether and *n*-heptane
k) *n*-butyl acetate and *n*-octane
l) *n*-butyl acetate and ethylene bromide

9. Calculate the saponification equivalent of an ester from the following data:

	WT. OF SAMPLE	STANDARD BASE		STANDARD ACID	
	g.	ml.	*N.*	ml.	*N.*
a)	0.2500	50 0	0.1	21.5	0.1
b)	0.2200	50 0	0.1	41.0	0 05
c)	0.2860	50 0	0.1	43.8	0 05
d)	0.01540	5.00	0.05	2.34	0 05
e)	0.01426	5 00	0.05	2.80	0.05
f)	1.536	20.0	1.11	24.6	0.54
g)	1.483	20.0	1.08	21.1	0.54
h)	1.335	20 0	0.95	16.0	0.54

10. Write the structure of an ester having a saponification equivalent of 116, and giving an acid which, when pure, has a neutralization equivalent of 88. Write all other possible structures.

11. Write the structure of an ester having a saponification equivalent of 80, and giving an acid which, when pure, has a neutralization equivalent of 61. Write all other possible structures.

12. Write the structure of an ester having a saponification equivalent of 102, and giving an alcohol that yields a yellow solid with dilute aqueous solutions of KI_3 and K_2CO_3 Write all other possible structures.

13. Compound *A*, slightly soluble in water and in cold dilute aqueous acids and bases, dissolved in conc. hydriodic acid. After heating in a sealed tube a second liquid, *B*, separated. This distilled at 72°. The reaction mixture was made neutral, then barium chloride added. From the preciptate *C*, treatment with sulfuric acid gave barium sulfate and a crystalline solid, m p. 153°. What was *A*?

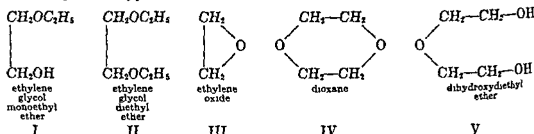
14. Compound *A*, $C_4H_{10}O$, with acetyl chloride gave *B*, $C_6H_{12}O_2$, and with chromic acid mixture, *C*, $C_4H_8O_2$. *C* with thionyl chloride gave *D*, C_4H_7OCl, which reacted with methanol to form *E*, $C_5H_{10}O_2$, boiling at 102°. What deductions can be drawn from these statements? Show how a structure for *A* can be worked out. Is any other structure possible?

15. Compound *A* is a liquid very slightly soluble in water, and in cold dilute aqueous acids and bases. It reacts very rapidly with bromine; by use of a standard solution of bromine in carbon tetrachloride, 0.2505 g. of *A* was found to absorb 0.3123 g of bromine, without evolution of hydrogen bromine. *A* slowly dissolved when refluxed with aqueous sodium hydroxide solution. Distillation of the resulting solution through a fractionating column gave a distillate which initially was composed of two phases. This gave iodoform with KI_3 and sodium carbonate. What deductions can be drawn from these statements? Show how a structure for *A* can be worked out.

CHAPTER 16 Ethers and Esters of Glycols and Glycerol

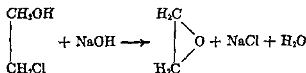
ETHERS

Ethers related to a glycol include mono- and di-ethers with monohydric alcohols (I and II), a mono- or di-ether with itself (III, IV, and V), and finally mono- and di-ethers with other di- and polyhydric alcohols. Examples of the most important types are shown below.

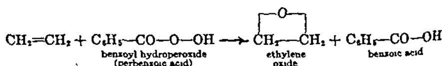


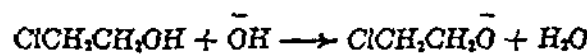
Ethylene oxide, because of the numerous reactions it undergoes, is the most interesting of these from a chemical point of view.

Ethylene Oxide, Epoxyethane, $(CH_2)_2O$. This is the simplest cyclic ether. It is formed when ethylene chlorohydrin is heated with aqueous strong base in concentrated solution.

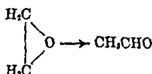


The reaction is essentially the Williamson synthesis of an ether, for the first step is the formation of a salt of the chlorohydrin. This is a general method for the preparation of olefin oxides (epoxides). Another general method is the action of a peroxyacid on an olefin.

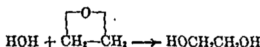


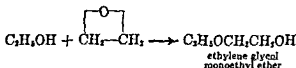


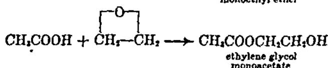
Because of the strain in the three membered ring (Chap. 7), ethylene oxide undergoes a number of reactions, with opening of the ring. When heated under pressure it rearranges to acetaldehyde.

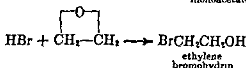


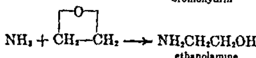
Ethylene oxide reacts with many compounds having active hydrogen (p. 127), for example, water, alcohols, acids, and ammonia. The reactions are catalyzed by a strong acid or a strong base.



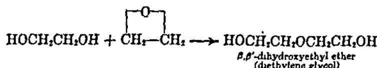






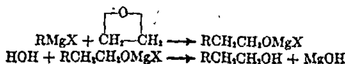


Ethylene glycol may react with ethylene oxide.

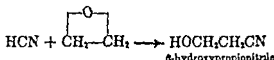


The reaction can continue, with formation of triethylene glycol and higher products.

An important reaction of ethylene oxide is the one with Grignard reagents, for in this way a normal carbon chain can be lengthened two carbon atoms at a time, and still leave a reactive group on the terminal carbon atom.



Another reagent which lengthens the carbon chain is hydrogen cyanide. The reaction requires heating (under pressure) and the addition of a base, to form cyanide ion.

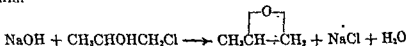


The reaction is useful in the preparation of unsaturated acids:

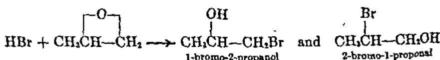
Many of the reactions of ethylene oxide resemble those of acetaldehyde. This will be evident from a study of the next chapter.

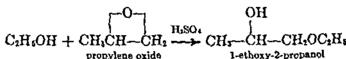
Ethylene oxide is toxic to insects, especially their eggs, and aids in the control of mold and bacteria in foods. As a protection against insect pests it is used in the fumigation of goods in storage, especially grain, furs, and household goods For this purpose it usually is mixed with carbon dioxide, which serves a double purpose in stimulating respiration in the animal organism, and in diminishing hazard from fire or explosion. Ethylene oxide is useful in organic synthesis, and in the manufacture of glycol derivatives.

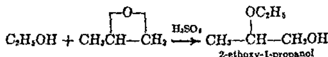
Other Epoxy Compounds: Propylene Oxide. This is prepared from propylene chlorohydrin.



It reacts like ethylene oxide, and adds many compounds having active hydrogen. Usually the hydroxyl group occupies the 2 position, but with acids or with other compounds under acid conditions, both possible products are formed.

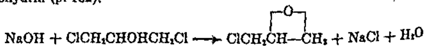




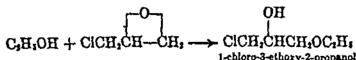


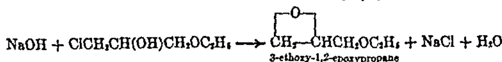
When the reaction is catalyzed by a very strong base, for example, sodium ethoxide, 1-ethoxy-2-propanol is the sole product.

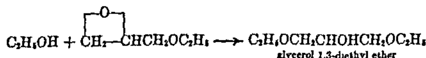
Epichlorohydrin, 3-Chloro-1,2-epoxypropane. This is prepared from glycerol dichlorohydrin (p. 162).



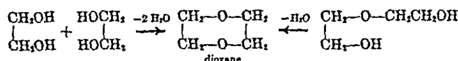
It undergoes the typical reactions of the 1,2-epoxy compounds, also displacement reactions of the chlorine atom. It is useful in making ethers and esters of glycerol.







Dioxane, 1,4-Dioxane, $\overline{CH_2CH_2OCH_2CH_2O}$. This is a cyclic diether of ethylene glycol. It may be prepared from either ethylene glycol or diethylene glycol by heating with a small amount (about 4%) of concentrated sulfuric acid, and distilling out the dioxane as it is formed. The reaction is a typical ether reaction, for it is catalyzed by a strong acid, and is reversible.



Dioxane coordinates with halogens, strong acids, and some salts. Typical compounds are $C_4H_8O_2 \cdot Br_2$, m.p. 66°, and $C_4H_8O_2 \cdot H_2SO_4$, m.p. 101°. Dioxane often serves as a solvent for carrying out reactions between organic and inorganic compounds, for many salts dissolve in it. It is miscible with water in all proportions.

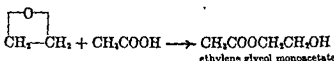
TABLE 54 | Some Glycol Oxides, Ethers, and Esters

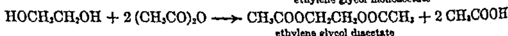
NAME	FORMULA	B.P. °C	SOLY. IN H_2O % BY WT.
Ethylene oxide	$\overline{CH_2CH_2O}$	10.7	misc.
1,4-Dioxane[a]	$O(CH_2CH_2)_2O$	101.1	misc.
[illegible]	[illegible]	244.8	misc.
[illegible]	[illegible]	178.5	1.1
[illegible]	[illegible]	125.0	misc.
[illegible]	[illegible]	135.1	misc.
[illegible]	[illegible]	171.2	misc.
[illegible]	[illegible]	121.4	21.0
[illegible]	[illegible]	188	
[illegible]	[illegible]	186.0	16.2
Propylene oxide	$CH_3\overline{CHCH_2O}$	34.1	41.0
Epichlorohydrin	$CH_2Cl\overline{CHCH_2O}$	117	

[a] m.p. 11°.

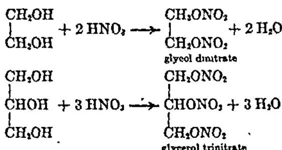
ESTERS OF MONOBASIC ACIDS

One or more of the hydroxyl groups of dihydric and polyhydric alcohols may be esterified. Glycol esters are much used as solvents, especially by the lacquer industry. The half esters are best prepared with the epoxy compound, the complete ester by use of an acid anhydride on the hydroxy compound, exemplified in the preparation of ethylene glycol monoacetate and diacetate.





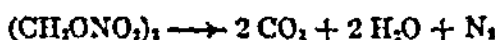
Nitrates. The nitrates are the most important of the simpler esters of glycols and of glycerol. They are manufactured by the controlled action of a mixture of anhydrous nitric and sulfuric acids (usually prepared from concentrated nitric acid and oleum, *i.e.*, fuming sulfuric acid).



These and other similar compounds are used as explosives. The instability is due to the fact that in the same molecule are the oxidizing element (nitrogen attached to oxygen) and the reducing elements (carbon and hydrogen). The powerful explosion is due to two factors: (1) rapid propagation of decomposition, once it is started; and (2) relatively large volume of hot, gaseous products. The gas is composed mainly of carbon monoxide, steam, and nitric oxide. An idealized equation can be written, which in the case of glycol dinitrate is the following.



However, other gaseous products are present, mainly nitrogen and carbon dioxide, the formation of which can be accounted for by another idealized equation.



Actually the decomposition is a complicated change and the composition of the gaseous mixture varies with changes in the temperature and pressure of the explosion. Although glycol dinitrate is safer to handle than glycerol trinitrate, for it is not so sensitive to shock, its greater volatility prevents its

wider use. Care is necessary when working with organic nitrates and nitrites. They cause dilation of capillaries, venules, and coronary blood vessels. Results are headache, flushing of the face, and drop in blood pressure.

Nitroglycerin is the usual name for glycerol trinitrate. It is not, structurally, a nitro compound (see Chap. 24). By itself it is an oily liquid that decomposes with explosive violence when heated to 180°. It is sensitive to shock and may detonate unexpectedly. Old samples during exposure to air may undergo hydrolysis, with development of free nitric acid This may cause spontaneous decomposition Nitroglycerin is much more stable when absorbed by porous material like silicious earth. This is **dynamite.** The discovery of dynamite was made in 1866 by Alfred Nobel, a Swedish engineer. From the fortune acquired in the manufacture of explosives he established the fund which makes possible the granting of the well-known Nobel prizes.

Fats. These are esters of glycerol with higher fatty acids, and often are called **glycerides.** They occur widespread in animals and plants. Some fats are solid, others are liquid. The latter often are called fatty oils. They sometimes are classified as fixed oils, for they are nonvolatile with steam, in contrast to the volatile oils, which distil with steam. Most fats can be used as food. Often these are referred to as edible fats and oils

Animal fats are separated from animal tissue by heating, usually with water or steam. Vegetable oils usually are separated from the comminuted seed or fruit by means of pressure. The better grade of oil is obtained by pressure in the cold, but recovery is improved if heat is applied. The resulting hot-drawn oil, however, is not as light colored as a cold-drawn oil and thus is less valuable. The press cake still contains 10 per cent or more of oil. This can be separated by solvent extraction, usually with petroleum ether or carbon disulfide. The oil so obtained can be used industrially, as in soap making, but is not satisfactory in food or medicine, because of the presence of residual solvent.

The acidic radicals present in fats are, except in a few rare cases, derived from straight-chain, monocarboxylic acids. Unsaturated acids are widely distributed in fats. The most important of these is the C_{18} acid, *viz.*, oleic acid. Among the relatively few acids that do not have a normal chain are the cyclic chaulmoogric and hydnocarpic acids (Chap. 26) from chaulmoogra oil, and tiglic acid from croton oil. The three most important acids are palmitic, stearic, and oleic acids.

The composition of some fats and oils is shown in Table 55. It will be noted that in a hard fat like beef tallow there is a relatively high percentage of glycerides of the higher saturated acids, palmitic and stearic, while in some oils and in soft fats like butter and lard there is a relatively large percentage of olein. Triolein melts at −17°, while tristearin melts at 71°. The low melting points of some other oils are due to the presence of other glycerides. Thus the acids from coconut oil contain much lauric acid, those from cottonseed oil contain much linoleic acid, and those from linseed oil much linoleic and linolenic acids.

The glycerides present in fats usually are not the simpler compounds, for example, tripalmitin and triolein, but rather mixed glycerides in which the glycerol molecule is combined with two or even three different acids. Only when there is a high percentage of a single acid does a fat contain much simple triglyceride.

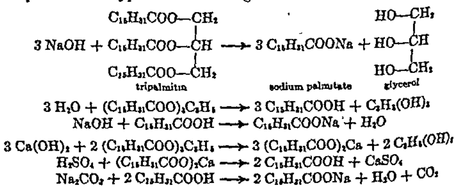
Fats and fatty oils are important industrial products and find extensive use in various industries such as food, lubrication, paint and varnish, linoleum, and soap. Most

animal and many vegetable fats and oils are edible. Their value here is due mainly to the fact that they supply twice as much energy as starch and protein (9.3 calories per gram, against 4.1 calories per gram for starch and protein). Highly unsaturated oils (linseed oil, tung oil) are not usually satisfactory as foods. Neither is castor oil, owing to its purgative action. However, it performs a service in medicine because of this property. Also, castor oil is a valuable lubricant. It often is added to lubricating oils derived from petroleum, in order to improve lubricating properties.

Linseed oil and tung oil are the principal drying oils and are widely used in paints and varnishes. These oils contain a high percentage of unsaturated glycerides, and on exposure to air form hard, firmly adhering films. The process is mainly polymerization, induced by oxidation. There is an actual though slight gain in weight, because of the oxygen absorbed. To accelerate the drying process the oil usually is given other treatment. Sometimes it is blown, that is, air is forced through it, to initiate the change, or a **dryer** may be added. This may be a metallic oxide, usually manganese or cobalt oxide, with which the oil must be heated to effect solution, or preferably it may be a salt of one of these metals with an organic acid, for example, a manganese or cobalt soap. The alkyl radical of the acid should be large, and the acid should have a reasonably low melting point, to insure that the salt is soluble in the oil. Spontaneous combustion may take place if oxidation of a drying oil is permitted *without dissipation of the heat evolved as, for example, with a pile of rags soaked in linseed oil.*

Linoleum is made by adding cork or other similar material to linseed oil which has been oxidized by air treatment until it has attained the consistency of jelly. Pigments are added to impart color.

Soaps. These embrace salts of fatty acids with heavy, as well as light, metals. The common soaps of commerce are sodium soaps and are manufactured from fats. There are three general methods of manufacture, the first of which is the classical standard method, the second is an increasingly important one, and the third appears to be of academic interest mainly: (1) saponification of the fat with sodium hydroxide; (2) catalytic hydrolysis of the fat to fatty acid and neutralization of this with sodium hydroxide; (3) saponification of the fat with lime, followed by metathesis, first with sulfuric acid, then with sodium carbonate. The conversion of tripalmitin to sodium palmitate is typical of the changes involved.



$$3\,NaOH + (C_{15}H_{31}COO)_3C_3H_5 \text{ (tripalmitin)} \longrightarrow 3\,C_{15}H_{31}COONa \text{ (sodium palmitate)} + HOCH_2CH(OH)CH_2OH \text{ (glycerol)}$$

$$3\,H_2O + (C_{15}H_{31}COO)_3C_3H_5 \longrightarrow 3\,C_{15}H_{31}COOH + C_3H_5(OH)_3$$

$$NaOH + C_{15}H_{31}COOH \longrightarrow C_{15}H_{31}COONa + H_2O$$

$$3\,Ca(OH)_2 + 2\,(C_{15}H_{31}COO)_3C_3H_5 \longrightarrow 3\,(C_{15}H_{31}COO)_2Ca + 2\,C_3H_5(OH)_3$$

$$H_2SO_4 + (C_{15}H_{31}COO)_2Ca \longrightarrow 2\,C_{15}H_{31}COOH + CaSO_4$$

$$Na_2CO_3 + 2\,C_{15}H_{31}COOH \longrightarrow 2\,C_{15}H_{31}COONa + H_2O + CO_2$$

In method (1) the fat and aqueous base are allowed to react, usually with heating. The fat quickly becomes emulsified, and in the dispersed state reacts readily. After

saponification more water is added, then sodium chloride. This "salts out" the soap, which is separated from the aqueous phase, dried, and pressed into the desired shape. Glycerol is recovered by evaporation of the water, followed by low pressure distillation of the glycerol. The salt present hinders complete recovery of the glycerol. In former years saponification often was carried out with potassium hydroxide, which many individuals prepared by causticizing wood ashes with lime. The resulting soap was called soft soap Potassium soaps are quite soluble in water and difficult to obtain in solid form. However, addition of sodium chloride to the aqueous solution salts out the less soluble sodium soap.

In method (2) hydrolysis is catalyzed by a naturally occurring ferment of the lipase type, or by a synthetic catalyst like the **Twitchell reagent.** An important function of the added substance is the ability to emulsify the fatty oil, so that there will be a large interfacial area. The temperature with lipase is kept about 35°, but with a synthetic catalyst may be higher. Lipase usually is obtained from the castor bean, which is one of the best sources. The Twitchell reagent is prepared by heating oleic acid, sulfuric acid, and an aromatic compound (naphthalene), so as to obtain a sulfonated fatty acid with some aromatic radical attached. After hydrolysis of the fat the fatty acids are skimmed off the surface of the water and are neutralized with sodium hydroxide. Economy results from the speed of reaction, smaller equipment, easy removal of the fatty acid, and easier recovery of glycerol, owing to the absence of dissolved salts.

Hydrolysis also is effected at high temperature. The fat and water are passed together at 225 to 250° under a pressure of about 700 pounds through a reactor. This process is becoming increasingly more important, because of the saving in time and equipment. No catalyst is necessary at these high temperatures.

In method (3) some economy is affected by the use of lime in place of sodium hydroxide. However, more operations are necessary, and these add to the cost.

Chemically a soap is a single salt, but actually soaps usually are mixtures of more than one salt, since they commonly are made from fats (see Table 55). Commercial soaps often are designated by the name of the corresponding fat, for example, coconut-oil soap and palm-oil soap. Castile soap is an olive-oil soap. Soaps made from liquid fats are more soluble than those made from solid fats.

Soluble soaps, for example, the sodium and potassium salts, are detergents, that is, cleansing agents. The cleansing action of a detergent results from the fact that it lowers the surface tension between water and an insoluble organic liquid such as an oil or fat. This is because its concentration in the surface layer of water is greater than in the rest of the liquid. When the surface tension is low, the surface area between water and oil can increase; when it has the normal value, the interfacial area tends to decrease. Emulsification of the oil takes place easily when the surface tension is low, and in the emulsified state the oil is removed with the water. Addition of acid often causes the emulsion to break. This is because the surface tension goes up when the soap is converted to the corresponding fatty acid by the added acid. The tendency then is for the interfacial area to decrease, which it does by the breaking of the emulsion, and the formation of larger drops of oil

Detergents are often spoken of as surface-active agents because they lower surface tension. In general, detergents have two distinguishing features: (1) a charged group, such as $-CO-\bar{O}$, $-SO_2-\bar{O}$, $-O-SO_2-\bar{O}$, $-\overset{+}{N}R_3$, and (2) a rather long hydrocarbon chain. The optimum length of an aliphatic chain in carboxylate and sulfate

TABLE 55 Approximate Composition of Fatty Acids from Some Fats [a]

FAT OR OIL	M.P. °C	SATURATED									UNSATURATED					
		C_4	C_6	C_8	C_{10}	C_{12}	C_{14}	C_{16}	C_{18}	$>C_{18}$	$<C_{16}$	C_{16}	C_{18}	C_{20}	$>C_{20}$	
Cod liver oil							3–6	6–11	0.5–1		0.5	11–20	25–30	26–32	10–19	
Salmon oil							3–5	11–15	1–2		0.5	9–10	25–29	23–26	16–20	
											MONOENOIC				LINOLEIC	LINOLENIC
											$<C_{16}$	C_{16}	C_{18}	$>C_{18}$		
Beef tallow	40–45					0.2	2–3	25–30	21–26	0 5–1	0.5	2–3	39–41	0.5	2	
Butter fat	28–33	3–4	1–2	1–2	2–4	3–5	9–11	22–30	7–15	0.5–1	1.5	4–5	29–40	0 3	3–5	
Coconut oil	21–24			8–9	4–8	45–51	17–18	7–9	1–3				5–8		1–2	
Cottonseed oil	3–4							20–23	1–3				24–30		42–54	
Lard	36–40						1–1.5	25–30	12–16		0 2	2–5	40–51	2–3	5–8	
Olive oil								7–15	4				70–85		4–12	
Palm oil																
seed				2–3	3–7	47–52	14–15	7–9	1				16–18		1	
fruit coat							1–4	35–45	1–8				40–50		2–11	
DRYING OILS																
Linseed oil							0.2	5 4	3.5	0 6			6–12		26–46	36–50
Tung oil																95 [b]

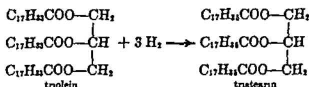
[a] All numbers except melting points are percentages.
[b] This is eleostearic acid, 9,11,13-octadecatrienoic acid, isomeric with linolenic acid.

salts is 12 or 14 carbon atoms. The charged end of the detergent molecule dissolves in water, the organic part dissolves in the oil.

Synthetic detergents have been increasing in popularity because they can be used in hard water, *i.e.*, water containing dissolved calcium or magnesium salts, without the formation of a precipitate, whereas ordinary soap forms a curdy precipitate. This is because magnesium and calcium soaps are insoluble in water while the magnesium and calcium salts of many alkyl sulfates and alkanesulfonic acids are water soluble. The advantage of detergents derived from amines and having a positively charged ion is inability to react at all with calcium or magnesium ion.

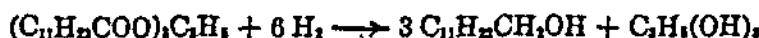
Salts of higher monocarboxylic acids with bivalent or trivalent metals are insoluble in water. In industry they are usually referred to as **metallic soaps.** They may be prepared either by heating fatty oils or fatty acids with the oxide, hydroxide, or carbonate of a metal, or by adding a solution of a soluble salt of the metal to a solution of a soluble soap, so as to obtain a precipitate of the insoluble soap. Lubricating greases are made by incorporating calcium or aluminum soaps with oils. Cobalt, manganese, and lead soaps are added to paint oils or to thinners, to act as dryers. Copper oleate and other similar substances act as waterproofing agents for fabrics. They are soluble in many organic solvents.

Hydrogenation and Hydrogenolysis of Fats. Nickel catalyzes hydrogenation at 50 to 150°, depending upon the activity of the catalyst Saturation of the double bonds converts olein to stearin.



In this way it is possible to cause fatty oils containing much olein, more especially the cheaper cottonseed oil and corn oil, to change to solid fat. The melting point can be regulated by controlling the extent of hydrogenation. In this way soft fats that resemble lard or butter in consistency are manufactured from oils ("Crisco," "Snowdrift").

Hydrogenolysis is effected in the presence of copper chromite, $CuCr_2O_4$, with hydrogen under pressures of 150 to 250 atmospheres and at temperatures of 200 to 300°. The acid radical is reduced. Any double bond is reduced also. Preferably the fat should contain considerable laurin, for lauryl alcohol is the most valuable of the higher alcohols.



Lauryl alcohol is the basis of an important group of detergents (p. 233).

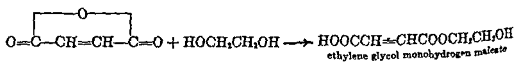
Reduction with metallic sodium and an alcohol (Bouveault-Blanc method) has become an important industrial process for the manufacture of lauryl alcohol (mixed with homologs) from coconut oil. A higher alcohol, methylisobutylcarbinol, for example, is preferred over ethyl alcohol, for there is less loss of sodium through formation of hydrogen. This method has the advantage over hydrogenolysis in leaving [illegible]

steapsin, which is elaborated in the pancreas and is discharged into the intestine as a constituent of the pancreatic juice. The glycerol and fatty acids pass through the intestinal wall, are reconverted into fat, and are transferred as such to various parts of the animal body to be used as needed, either to furnish energy or be stored. The fatty acid molecule is degraded two carbon atoms at a time while being oxidized in the body, and the product is an acid having two less carbon atoms. The oxidation involves scission of the carbon chain between the α- and β-carbon atoms. Since fats contain only acids with even-numbered carbon atoms, the oxidation finally proceeds through butyric and acetic acids.

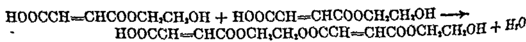
Analysis of Fats. Different fats are differentiated by means of various physical constants and by a number of chemical characteristics which indicate the nature of the constituent fatty acids. The *saponification number* is the number of milligrams of potassium hydroxide required to saponify one gram of fat. It is, of course, related to the mean molecular weight of the fat The *iodine number* is the percentage by weight of iodine that is absorbed by a given fat. This is a measure of the amount of unsaturation. The reagents used generally contain bromine as well as iodine; for the absorption of bromine is more complete than that of iodine. The *Reichert-Meissl number* is the number of milliliters of tenth-normal alkali required to neutralize the water-soluble volatile acids obtained from 5 grams of a fat. This test distinguishes butter from other fats because it has a higher value than any of the other fats. (Butter fat is 22–30, lard is 0.5.) Other constants are the *Hehner number,* which expresses the relation between the water-soluble volatile acids and the water-insoluble volatile acids; the *Polensky number,* which is related to the insoluble volatile acids, etc.

ESTERS OF DIBASIC ACIDS

In general, glycols (or glycerol) can react with dibasic acids to produce polyesters of high molecular weight. An excellent way to initiate the reaction is to start with the anhydride of the acid, for example, maleic anhydride.

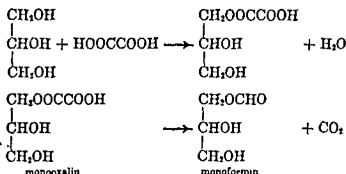


Since the reaction product contains both carboxyl and hydroxyl groups, two molecules can react, by elimination of water.

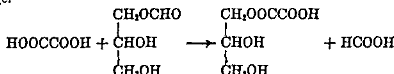


If heating is prolonged, the reaction continues and the product becomes a thick, viscous liquid. This is a linear polymer of high molecular weight. Other glycols may replace ethylene glycol and other dibasic acids may replace maleic acid, especially succinic and phthalic acids. The products are called alkyd resins, and are used in paints and varnishes. In order to improve hardness a small amount of other compound is added to promote cross linkage. This may be a tri- or polycarboxylic acid or a tri- or polyhydric alcohol.

Glycerol and Oxalic Acid. When glycerol and oxalic acid are heated, monooxalin (glycerol monooxalate) is formed, but this slowly decomposes above 100° to monoformin with evolution of carbon dioxide (see Oxalic Acid, p. 190).



On the addition of more oxalic acid, and heating, formic acid distils, owing to ester interchange.



The resulting monooxalin can decompose, as above. The operation can be repeated many times with the result that oxalic acid decomposes to formic acid. In case hydrated oxalic acid is added, some of the monoformin undergoes hydrolysis with regeneration of glycerol. This then reacts with oxalic acid as water and formic acid distil. This is a convenient laboratory method of preparing formic acid. The process actually is more complicated than shown, for other esters are present, especially dioxalin and diformin.

Rapid distillation of monoformin, obtained more conveniently from glycerol and formic acid, leads to the formation of allyl alcohol, which is best prepared this way.



$$HCO{-}OCH_2CH(OH)CH_2OH \longrightarrow CH_2{=}CHCH_2OH + CO_2 + H_2O$$

PROBLEMS

1. Starting with ethylene, and using any reagents desired, show the steps involved in a synthesis of the following derivatives of ethylene glycol:

a) monomethyl ether
b) monoisopropyl ether
c) dimethyl ether
d) methylisopropyl ether
e) monopropionate
f) dipropionate
g) mono-n-butyrate
h) di-n-butyrate
i) acetate-propionate
j) propionate-butyrate
k) monomethyl ether acetate
l) mono-β-hydroxyethyl ether

2. Starting with ethyl alcohol as the only organic compound, show the steps involved in a practical synthesis of:

a) β-ethoxyethyl ether
b) β-chloroethyl ether
c) β-acetoxyethyl ether
d) β,β'-dichloroethyl ether
e) β,β'-dihydroxyethyl ether
f) β-bromoethyl ether
g) β-iodoethyl ether
h) β-chloroethyl acetate
i) 1-bromo-2-acetoxyethane
j) 1,2-diacetoxyethane
k) 2-(2-chloroethoxy)-1-ethanol
l) 2-(2-bromoethoxy)-1-ethanol
m) β-chloroethyl β-hydroxyethyl ether
n) β-chloroethyl β-ethoxyethyl ether

3. Starting with ethyl alcohol, isopropyl alcohol, and acetic acid as the only organic compounds, show the steps involved in a practical synthesis of:

a) 1-chloro-2-hydroxypropane
b) 1-amino-2-hydroxypropane
c) 1-bromo-2-hydroxypropane
d) 1-ethoxy-2-hydroxypropane
e) 1-acetoxy-2-hydroxypropane
f) 1-hydroxy-2-isopropoxyethane
g) 1-chloro-2(2-hydroxyethoxy)-propane
h) 1-chloro-2(2-hydroxypropoxy)-propane
i) 1-isopropoxy-2-acetoxyethane
j) 1(2-hydroxyethoxy)-2-hydroxypropane

4. Starting with glycerol, and using any other compounds, show the steps involved in a practical preparation of:

a) 1-acetoxy-3-chloro-2-propanol
b) 1-methoxy-3-chloro-2-propanol
c) 1,3-di-*n*-propoxy-2-propanol
d) 1,3-di-*n*-butoxy-2-propanol
e) 1-methoxy-3-acetoxy-2-propanol
f) 1-methoxy-3-*n*-butoxy-2-propanol
g) 1-ethoxy-3-acetoxy-2-propanol
h) 3-propionoxy-1,2-propanediol

5. Write balanced equations, with structural formulas, showing how the following crude products could be obtained from crude glycerides (give name of source):

a) barium stearate (one step)
b) lead oleate (one step)
c) calcium laurate (one step)
d) copper oleate (by precipitation)
e) zinc stearate (by precipitation)
f) aluminum palmitate (by precipitation)
g) cobalt linoleate (by precipitation)
h) manganese linoleate (by precipitation)

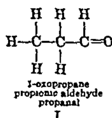
6. Show the steps involved in the preparation of the following from a glyceride (name the crude source) using only inorganic reagents:

a) lauryl laurate
b) hexadecyl palmitate
c) stearic anhydride
d) sodium lauryl sulfate
e) potassium octadecyl sulfate
f) 1-bromo-9-octadecene

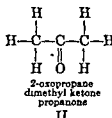
CHAPTER 17

Aldehydes and Ketones

Saturated aldehydes and ketones are oxo (keto) derivatives of alkanes, they have a carbonyl (oxo) group in place of two hydrogen atoms, and their formulas correspond to the general formula, $C_nH_{2n}O$. In them the oxygen atom is attached to a carbon atom by a double bond. When the oxo group is attached to a terminal carbon atom the compound is an aldehyde, and to some other carbon atom, a ketone. Thus 1-oxopropane, I, is propionaldehyde, and 2-oxopropane, II, is dimethyl ketone.



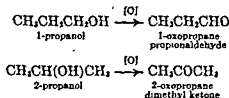
1-oxopropane
propionic aldehyde
propanal
I



2-oxopropane
dimethyl ketone
propanone
II

Chemically aldehydes and ketones resemble each other in undergoing many similar reactions. However, they differ in that aldehydes react more readily, and moreover undergo some reactions, for example, polymerization, that ketones do not show. This difference in chemical reactivity is great enough to justify a separate classification of the two.

Structures of Aldehydes and Ketones. The structures of propionaldehyde, I, and dimethyl ketone, II, are established by methods of preparation and by their chemical behavior. They are obtained by oxidation of the two propyl alcohols, the primary alcohol yielding propionaldehyde, the secondary yielding acetone.

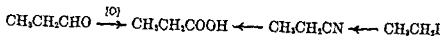


$$\underset{\text{1-propanol}}{CH_3CH_2CH_2OH} \xrightarrow{[O]} \underset{\substack{\text{1-oxopropane}\\\text{propionaldehyde}}}{CH_3CH_2CHO}$$

$$\underset{\text{2-propanol}}{CH_3CH(OH)CH_3} \xrightarrow{[O]} \underset{\substack{\text{2-oxopropane}\\\text{dimethyl ketone}}}{CH_3COCH_3}$$

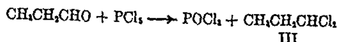
Moreover, the presence of an ethyl radical in I is established by another reaction, *viz.*, its oxidation to propionic acid. The formation of this acid from

ethyl iodide by the nitrile synthesis proves the presence of the ethyl radical in the acid.

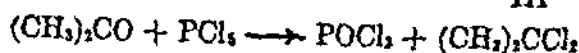


$$CH_3CH_2CHO \xrightarrow{[O]} CH_3CH_2COOH \longleftarrow CH_3CH_2CN \longleftarrow CH_3CH_2I$$

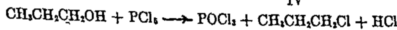
Evidence that the oxygen atom is attached to one carbon only is obtained by the reaction of phosphorus pentachloride, which gives 1,1-dichloropropane, III, with propionaldehyde, and 2,2-dichloropropane, IV, with dimethyl ketone. It will be recalled that when phosphorus pentachloride reacts with an alcohol, the hydroxyl group is replaced by one chlorine atom; for example, 1-propanol gives 1-chloropropane, V.



$$CH_3CH_2CHO + PCl_5 \longrightarrow POCl_3 + \underset{\text{III}}{CH_3CH_2CHCl_2}$$



$$(CH_3)_2CO + PCl_5 \longrightarrow POCl_3 + \underset{\text{IV}}{(CH_3)_2CCl_2}$$



$$CH_3CH_2CH_2OH + PCl_5 \longrightarrow POCl_3 + \underset{\text{V}}{CH_3CH_2CH_2Cl} + HCl$$

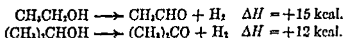
Thus the oxygen atom in an aldehyde or ketone is linked to the carbon atom by a double bond, and cannot be part of a hydroxyl group. The evidence, therefore, establishes I as the structure of propionaldehyde, and II as the structure of dimethyl ketone.

In order to avoid confusion with the hydroxyl group it is customary to write the aldehyde group as CHO, not COH.

Nomenclature of Aldehydes and Ketones. The word *aldehyde* is an abbreviation of the earlier term *alcohol dehydrogenatus*, or alcohol less hydrogen. In one system an aldehyde is named from the acid which it yields on oxidation; *i.e.*, CH_3CH_2CHO is propionic aldehyde (or propionaldehyde) since it yields propionic acid when oxidized, and a ketone is named from the alkyl radicals in combination with the carbonyl group, *i.e.*, $CH_3COCH_2CH_3$ is methyl ethyl ketone. The smaller of two dissimilar radicals is named first. In the I.U.C. system an aldehyde is named by changing the terminal -e of the hydrocarbon to -al, *i.e.*, CH_3CH_2CHO is propanal, while a ketone is named by changing the final -e to -one, *i.e.*, CH_3COCH_3 is propanone. In case two isomers are possible, the position of the oxygen is indicated by a numeral: $CH_3COCH_2CH_2CH_3$ is 2-pentanone. In a third system of nomenclature no distinction is made between aldehydes and ketones, but both are designated as oxo derivatives, the position of the oxygen atom being indicated by number. Butyraldehyde is 1-oxobutane, *n*-valeraldehyde is 1-oxopentane, and 2-pentanone is 2-oxopentane.

Preparation of Aldehydes and Ketones. Acetaldehyde, CH_3CHO, will be used as a typical aldehyde, and acetone, CH_3COCH_3, as a typical ketone. Formaldehyde, the first member of the aldehyde series, differs in some respects from the other members. Of the methods described, 1 to 7 are common to both aldehydes and ketones, 8 to 11 are applicable to aldehydes, and 12, 13, and 14, to ketones.

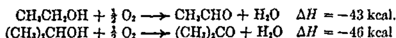
1. *Dehydrogenation of alcohols.* When the vapor of an alcohol is passed over a suitable catalyst at an elevated temperature (250–400°), dehydrogenation takes place. The energy changes below are calculated from bond energies.



$$CH_3CH_2OH \longrightarrow CH_3CHO + H_2 \quad \Delta H = +15 \text{ kcal.}$$
$$(CH_3)_2CHOH \longrightarrow (CH_3)_2CO + H_2 \quad \Delta H = +12 \text{ kcal.}$$

The reactions are endothermic, and equilibrium conditions at room temperature favor the alcohol (see p. 146). A rise in temperature causes the equilibrium to shift in favor of the dehydrogenation reaction. Ketones are produced from secondary alcohols in industry by this reaction. Many types of catalysts are effective, among the most satisfactory being copper-silver alloy, copper-zinc alloy, and metallic rhenium. Since aldehydes at elevated temperatures decompose in other ways more easily than do ketones (p. 261), they are not easily obtained by dehydrogenation.

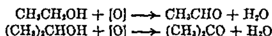
2. *Catalytic gas phase oxidation of alcohols.* A primary or secondary alcohol undergoes partial oxidation when the vapor, mixed with a limited amount of oxygen or air, is passed over a heated catalyst (p. 147). The reaction is strongly exothermic, owing to the formation of water vapor; the values below are calculated from bond energies.



$$CH_3CH_2OH + \tfrac{1}{2} O_2 \longrightarrow CH_3CHO + H_2O \quad \Delta H = -43 \text{ kcal.}$$
$$(CH_3)_2CHOH + \tfrac{1}{2} O_2 \longrightarrow (CH_3)_2CO + H_2O \quad \Delta H = -46 \text{ kcal}$$

On account of the strongly exothermic nature of the reaction, conditions must be carefully controlled. Industrially, secondary alcohols are catalytically oxidized to ketones. Methanol reacts more readily than other alcohols. Spongy platinum, an especially effective catalyst, promotes reaction between methanol vapor and air at the ordinary temperature.

3. *Oxidation of alcohols with an oxidizing agent.* One of the most commonly used reagents in the laboratory is "chromic acid mixture," a dichromate in aqueous sulfuric acid (p. 147). This is a convenient laboratory method.



$$CH_3CH_2OH + [O] \longrightarrow CH_3CHO + H_2O$$
$$(CH_3)_2CHOH + [O] \longrightarrow (CH_3)_2CO + H_2O$$

Ketones usually result in good yield, but aldehydes are more susceptible to oxidation. Volatile aldehydes usually can be obtained in satisfactory yield, for they can be removed from the reaction mixture as formed.

4. *Pyrolysis of calcium salts.* When the dry calcium salt of a carboxylic acid is heated, calcium carbonate and a ketone are formed. This is a convenient method for ketones.



$$CH_3COO\text{----}Ca\text{----}OCOCH_3 \longrightarrow CaCO_3 + CH_3COCH_3$$

In general, barium salts of carboxylic acids decompose similarly. An unsymmetrical ketone can be prepared from a mixture of calcium salts.



$$CH_3COO\text{----}Ca\text{----}OCOC_2H_5 \longrightarrow CaCO_3 + CH_3COC_2H_5$$

If one of the salts is calcium formate an aldehyde is formed, but usually the yield is very poor.



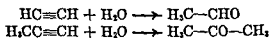
Many other salts yield ketones also, for example, magnesium, manganese, zinc, cerium, and thorium.

5. *Decarboxylation of carboxylic acids.* When the vapor of a carboxylic acid is passed over calcium or barium carbonate at temperatures near 450°, carbonic acid and a ketone are formed (p. 176).

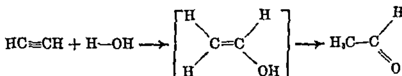


Presumably the barium salt is an intermediate. Carbonates or oxides of many other metals act similarly. Manganous oxide is one of the best. Unsymmetrical ketones are formed from a mixture of two acids, and aldehydes result if one of the acids is formic. Reaction products are mixtures.

6. *Hydration of alkynes.* Only one alkyne, *viz.*, acetylene, yields an aldehyde; a homolog yields a ketone (p. 84). Acetaldehyde is produced industrially from acetylene by hydration in dilute aqueous sulfuric acid containing mercuric sulfate.

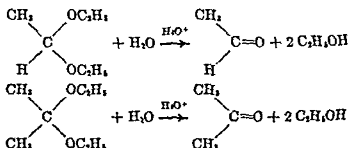


It is believed that the first step in the hydration of acetylene is the formation of vinyl alcohol, which then rearranges to acetaldehyde.

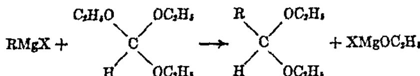


The hydration of propyne follows Markownikoff's rule and proceeds by a similar mechanism.

7. *Hydrolysis of acetals and ketals.* These undergo hydrolysis under acidic conditions.



Usually acetals and ketals are prepared from the corresponding oxo compound. However, acetals may be synthesized by the action of Grignard reagents with ethyl orthoformate.



8. *Hydrogenolysis of acyl chlorides.* One of the most satisfactory methods for higher aldehydes is the action of hydrogen on an acyl chloride in boiling xylene (130°), in the presence of a poisoned palladium catalyst on barium sulfate (p. 218).

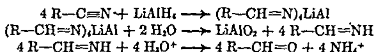


The course of the reaction is followed by determining the amount of hydrogen chloride evolved.

9. *Reduction of nitriles.* Nitriles with stannous chloride and hydrogen chloride in absolute ether yield addition compounds of stannic chloride with aldimine hydrochlorides. The latter, on the addition of water, are rapidly hydrolyzed to aldehydes and ammonia (p. 392)



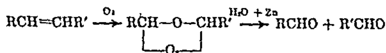
Nitriles are reduced by lithium aluminum hydride at Dry Ice temperature to aldimine salts. These undergo hydrolysis to aldehydes in dilute aqueous acid.



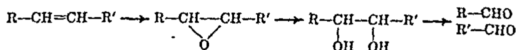
10. *Depolymerization.* Some aldehydes (acetaldehyde and propionaldehyde especially) are conveniently prepared by heating the corresponding trimer with a small amount of sulfuric acid, which acts catalytically.



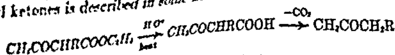
11. *Oxidation of alkenes or glycols.* Ozonides of alkenes when decomposed by water in the presence of zinc dust yield aldehydes. This ozonolysis reaction is of value mainly in structural determination of alkenes (p. 200); it might be useful for preparing aldehydes.



A more convenient method involves conversion of alkenes to the corresponding glycols (p. 159), followed by oxidative cleavage to aldehydes (p. 161).

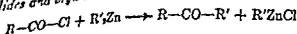


12. *Decomposition of acetoacetic esters.* This useful general method for methyl ketones is described in some detail in Chapter 19, p. 330.



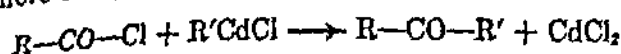
$$CH_3COCHRCOOC_2H_5 \xrightarrow[\text{heat}]{H^+} CH_3COCHRCOOH \xrightarrow{-CO_2} CH_3COCH_2R$$

13. *Acyl halides and organometallic compounds* (see pp. 132, 219).



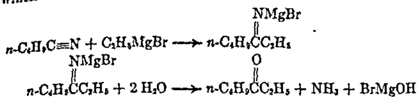
$$R{-}CO{-}Cl + R'_2Zn \longrightarrow R{-}CO{-}R' + R'ZnCl$$

Alkylcadmium halides are even more useful than the dialkylzincs, for they *are prepared more easily.*



$$R{-}CO{-}Cl + R'CdCl \longrightarrow R{-}CO{-}R' + CdCl_2$$

14. *Higher nitriles and Grignard reagents.* These give derivatives of ketimines which on hydrolysis are converted to ketones.



$$n\text{-}C_4H_9C{\equiv}N + C_2H_5MgBr \longrightarrow n\text{-}C_4H_9C({=}NMgBr)C_2H_5$$

$$n\text{-}C_4H_9C({=}NMgBr)C_2H_5 + 2\,H_2O \longrightarrow n\text{-}C_4H_9C({=}O)C_2H_5 + NH_3 + BrMgOH$$

15. *Special methods.* Most important of these are the formation of acetone in "wood distillation" and by starch fermentation processes, described under Acetone (p. 283).

Physical Properties of Aldehydes and Ketones. Some of these properties are listed in Tables 56 and 57. Most of the compounds are liquids

TABLE 56 | **Physical Constants of Some Normal Aldehydes**

NAME	FORMULA	M.P. °C	B.P. °C	SP. GR. 20/4	SOLUBILITY IN WATER G./100 G.	HEAT OF COMBUSTION (C_v) KCAL./MOLE
Formaldehyde	HCHO	−92.0	−21 0	0.815^{-20}	v. sol.	134 1
Acetaldehyde	CH_3CHO	−121	20 2	.781	misc.	274 8
		−81.0	48 8	.807	16	433 8
		−99.0	75.7	817	7	
		−91.5	103.4	$.819^{11}$	s. sol.	
			131	.834	s. sol.	
		−42.0	155.0	.850	0.124	
			81.0^{22}	.821	s. sol.	

Solids are not usually encountered until there are about twelve carbon atoms in the molecule. The lowest members are miscible with water. The way water solubility drops as the carbon content rises is typified by the methyl ketones. On the average the solubility drops about one third with each ad-

ditional carbon atom. Aldehydes and ketones are more soluble in aqueous solutions of strong acids than they are in water. This is because, like alcohols, they are weakly basic and accept protons, forming oxonium salts.

TABLE 57 | Physical Constants of Some Normal Ketones

NAME	FORMULA	M.P. °C	B.P. °C	SP. GR. 20/4	SOLUBILITY IN WATER G./100 G.	HEAT OF COMBUSTION (C_v) KCAL./MOLE
A. SYMMETRICAL KETONES						
Dimethyl	$(CH_3)_2CO$	−94.3	56.1	.7915	misc.	426.3
Diethyl	$(C_2H_5)_2CO$	−41.5	101.0	.814	5	740.5
Dipropyl	$(C_3H_7)_2CO$	−32.6	143.5	.821[15]	s. sol.	1059.4
Dibutyl	$(C_4H_9)_2CO$		182	.827[15]	s. sol.	
Diamyl	$(C_5H_{11})_2CO$	14.6	226.3	.826	s. sol.	
B. METHYL KETONES						
Dimethyl	$(CH_3)_2CO$	−94.3	56.1	.7915	misc.	426.2
Methyl ethyl	$CH_3COC_2H_5$	−86.4	79.6	.8050	25.0[20]	[illegible]
Methyl propyl	$CH_3COC_3H_7$	−77.8	101.7	.8089	6.3[20]	[illegible]
Methyl butyl	$CH_3COC_4H_9$	−56.9	127.2	.8200	3.5[20]	[illegible]
Methyl amyl	$CH_3COC_5H_{11}$	−35.5	150.0	.8268	2.0[20]	
Methyl hexyl	$CH_3COC_6H_{13}$	−20	173		s. sol.	[illegible]

Aldehydes and ketones boil at lower temperatures than the corresponding alcohols and acids and at higher temperatures than the corresponding hydrocarbons. These relationships are shown in Table 58, along with the respective

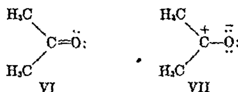
TABLE 58 | Some Three-Carbon Compounds

NAME	FORMULA	B.P. °C	DIPOLE MOMENT D
Propane	$CH_3CH_2CH_3$	−44	0.0
Methyl ethyl ether	$CH_3OCH_2CH_3$	[illegible]	
Propylene oxide	$CH_3(CHCH_2)O$	[illegible]	1.9
Propionaldehyde	CH_3CH_2CHO	[illegible]	2.7
Methyl acetate	CH_3COOCH_3	[illegible]	1.7
Acetone	CH_3COCH_3	[illegible]	2.8
Isopropyl alcohol	$CH_3CHOHCH_3$	[illegible]	1.7
n-Propyl alcohol	$CH_3CH_2CH_2OH$	[illegible]	[illegible]
Propionic acid	CH_3CH_2COOH	[illegible]	[illegible]

lectric dipole moments. The [illegible] though having [illegible]
ipole moments, are not as highly [illegible] the acid and the [illegible]
hich hydrogen bonding is [illegible]

gen attached to carbon does not form strong hydrogen bonds. However, the higher boiling points of the two oxo compounds in comparison to those of the ester, ether, oxide, and hydrocarbon, show that intermolecular attraction in the former two is greater than in the others. This may be due to weak hydrogen bonding, to dipolar attraction (Table 13, p 31) or to a combination of these.

The relatively high values of the dipole moments of propionaldehyde and acetone (Table 58) are important in connection with the chemical reactivity of these and similar compounds. It will be recalled (Chap. 3) that the molecular dipole moment is the resultant of the bond dipole moments. Since the bond dipole moment of the C—H bond is only 0.4 *D* (Table 15, p. 33) the high values of propionaldehyde and acetone must be due to the carbonyl bond, the dipole moment of which is 2.5 *D* (Table 15). From this figure it is possible to obtain an approximate value for the per cent of ionic character. For this purpose the assumption is made that if the C=O double bond were purely covalent, as in VI, its dipole moment would be zero, and if it were ionic, as in VII, its dipole moment would be 5.9 *D* (see p. 32). The per cent of ionic character is thus $2.5 \times 100/5.9$, approximately 45.



The contribution of VII to the overall structure is almost as important as that of VI, even though in VII the carbon atom has only a sextet of electrons. As the molecule absorbs energy, the contribution of VII becomes even more important, since this has the higher energy content. Thus the carbonyl carbon atom of acetone is strongly electrophilic since it is deficient in electrons. It has a strong tendency to form a bond with an unshared electron pair of some other atom.

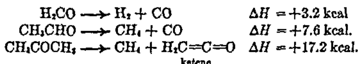
Reactions of Aldehydes and Ketones. Aside from pyrolysis, halogenation, nitrosation, alkylation, and oxidation, reactions are mainly those of addition to the carbonyl bond, C=O, or of condensation (addition followed by elimination of a molecule of some simple substance, usually water). Since dehydrogenation of alcohols with production of the carbonyl bond is accompanied by absorption of energy (p. 255), the reverse reaction of hydrogenation is an exothermic reaction. Thus the unsaturated bond tends to become saturated not only with hydrogen but also with many other reagents. In comparison to the olefinic double bond, C=C, the carbonyl bond is more easily formed, that is, less energy is absorbed on dehydrogenation. It is significant that the reversal of the addition of hydrogen, *i.e.*, dehydrogenation, is more easily accomplished in the case of alcohols than of paraffins.

Reagents adding readily to carbonyl bonds are those that can furnish an electron pair. The most reactive reagents of this type are carbanions and

as the alkynide ions of sodium salts of alkynes and the alkide ions of organometallic compounds. Less reactive are cyanide ion, bisulfite ion, ammonia, many ammonia derivatives, alcohols, water, and hydrohalic acids. Substances which react with the carbonyl bond are thus mainly nucleophilic reagents. Electrophilic reagents, for example halogens, do not attack the carbonyl bond. This last is in marked contrast to the behavior of the olefinic double bond.

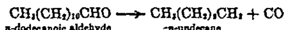
The reactions of aldehydes and ketones are described together, acetaldehyde, CH_3CHO, and acetone, $(CH_3)_2CO$, being taken as typical compounds. Formaldehyde, HCHO, the first member of the series, differs in some respects from other aldehydes.

1. *Pyrolysis.* When heated sufficiently (600° or higher) aldehydes and ketones decompose. The decomposition of formaldehyde, acetaldehyde, and acetone proceeds mainly in accordance with the equations below. The energy changes are calculated from bond and resonance energies.



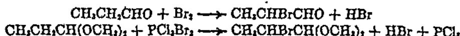
$$H_2CO \longrightarrow H_2 + CO \qquad \Delta H = +3.2 \text{ kcal}$$
$$CH_3CHO \longrightarrow CH_4 + CO \qquad \Delta H = +7.6 \text{ kcal.}$$
$$CH_3COCH_3 \longrightarrow CH_4 + \underset{\text{ketene}}{H_2C{=}C{=}O} \qquad \Delta H = +17.2 \text{ kcal.}$$

Many higher saturated aldehydes undergo a similar decomposition on exposure to ultraviolet light.



$$\underset{n\text{-dodecanoic aldehyde}}{CH_3(CH_2)_{10}CHO} \longrightarrow \underset{n\text{-undecane}}{CH_3(CH_2)_9CH_3} + CO$$

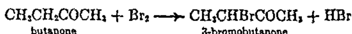
2. *Halogenation; the haloform reaction.* Ketones react more satisfactorily than aldehydes, since the latter may undergo other reactions, such as oxidation, polymerization, or condensation. Usually acetals of aldehydes give better results than the aldehydes themselves since side reactions are not so extensive. Substitution takes place in the *alpha*-position. Thus propionaldehyde with bromine in aqueous acetic acid gives α-bromopropional; propionaldehyde dimethylacetal with phosphorus trichloridedibromide gives α-bromopropionaldehyde dimethyl acetal.



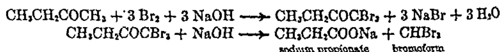
$$CH_3CH_2CHO + Br_2 \longrightarrow CH_3CHBrCHO + HBr$$
$$CH_3CH_2CH(OCH_3)_2 + PCl_3Br_2 \longrightarrow CH_3CHBrCH(OCH_3)_2 + HBr + PCl_3$$

Acetone with chlorine in diffused light yields unsymmetrical tetrachloroacetone, and in direct sunlight the completely substituted product. Acetone can be brominated to pentabromoacetone. In the presence of water the reactions take place more slowly. Both acid and base accelerate the rate of halogenation in aqueous solution. Under acid conditions the stepwise products can be isolated. Under basic conditions the reactions are more complicated. With acetone and bromine, for example, the first product usually is the unsymmetrical tribromo derivative. Preparation of monobromo derivatives of the lower ketones usually is carried out in water in which calcium

carbonate is suspended. This prevents too high an acid concentration. Under these conditions higher methyl ketones react almost entirely at a methylene group.

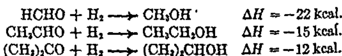


The **haloform reaction** takes place when halogenation of acetaldehyde or of a methyl ketone is carried out in aqueous basic solution (carbonate or hydroxide), usually warm. The final products are a trihalomethane (chloroform, bromoform, or iodoform) and a salt of a monocarboxylic acid. The intermediate trihalogeno compound is cleaved by the base.



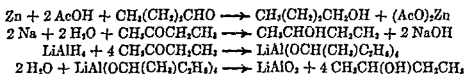
Chloroform and iodoform result when bromine is replaced respectively by chlorine and iodine. Alcohols that are oxidized by the reagent to acetaldehyde or to a methyl ketone also undergo the haloform reaction, for example, ethyl, isopropyl, and *sec*-butyl alcohols.

3. *Hydrogenation; reduction with hydrogen.* In the presence of colloidal platinum, aldehydes and ketones are reduced at room temperature. With Raney nickel, a less active catalyst, usually a somewhat higher temperature is required.

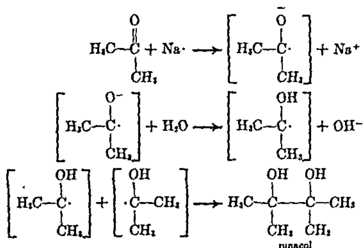


Aldehydes yield primary alcohols; ketones, secondary alcohols. The reactions are the reverse of the dehydrogenation of alcohols (p. 146). The equilibria, except at much higher temperatures, lie well on the side of the alcohols, as would be expected in view of the ΔH values given above. These values, calculated from bond energies, are for gaseous reactions. The relative values are important in showing that the reactions are more exothermic in the order: acetone < acetaldehyde < formaldehyde. In general, addition of a given reagent to the carbonyl bond would be expected to show a similar relationship. This explains the usual greater reactivity of formaldehyde relative to other aldehydes, and of aldehydes relative to ketones, in many addition and condensation reactions.

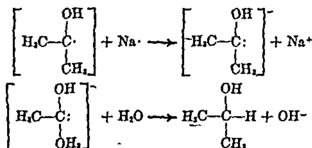
4. *Reduction.* Aldehydes and ketones can be reduced to the corresponding alcohols by the action of metallic sodium, sodium amalgam, or other active metal (aluminum amalgam) in the presence of water or other solvent (alcohol) to furnish hydrogen. Since a high alkalinity is not desirable, especially in the case of aldehydes, usually buffering or the addition of an acid is necessary. Sometimes aldehydes are reduced with zinc dust and acetic acid. Lithium aluminum hydride is a fast reducing agent and gives good yields of alcohols.



In the case of a ketone a side reaction in the reduction with metallic sodium leads to the production of pinacol, a tertiary glycol. This is believed to result from the union of two free radicals, or of two free radical ions, intermediates in the reduction process.

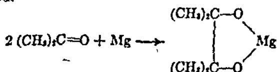


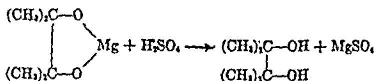
Thus the first step in the reduction process is the transfer of an electron from the sodium atom to the acetone molecule. The intermediate free radical either may couple to form pinacol or it may accept another electron and be reduced to the alcohol.



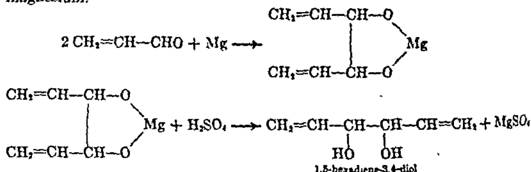
The overall change in reduction to the alcohol is equivalent to hydrogenation, that is, addition of a molecule of hydrogen to the double bond.

Pinacol is the main reaction product when anhydrous acetone is heated with amalgamated magnesium. The magnesium salt of pinacol is first formed, and when this is decomposed by the addition of water or of an aqueous acid, pinacol is liberated.

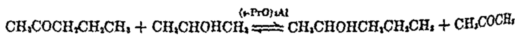




Unsaturated aldehydes also can be reduced to pinacols with amalgamated magnesium.

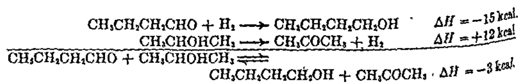


The Meerwein-Ponndorf method of reducing aldehydes and ketones involves heating with isopropyl alcohol containing aluminum isopropoxide. A higher ketone, 2-pentanone, for example, may be reduced to 2-pentanol. The aluminum is distributed between the two alcohols.



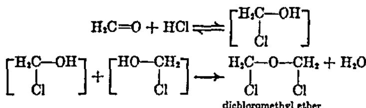
The system comes to equilibrium. The reaction can be driven toward the right by removal of the most volatile component, acetone.

If a higher aldehyde is to be reduced, equilibrium conditions favor the reaction to the right, because of differences in heats of reaction.

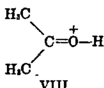


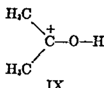
Thus an aldehyde is more easily reduced than a ketone. The method is much used for reducing an aldehyde or a ketone having a functional group that might be affected by other reducing agents as, for example, a double bond or a nitro group.

5. *Addition of strong acids.* The first reaction is a rapid coordination of a proton, with formation of a positive ion, as in the case of other oxygen compounds, such as alcohols (p. 142) and esters (p. 217). Subsequently, as may happen with hydrogen chloride, the negative ion may become attached to the carbon atom. However, compounds so formed usually are unstable, for equilibrium conditions favor the reactants. Indication of the formation of such an intermediate is shown by the formation of dichlorodimethyl ether when hydrogen chloride and formaldehyde vapor react.



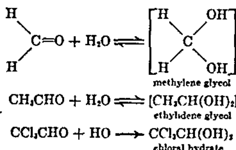
The formation of an onium complex could take place in aqueous solution, but in that case only a fraction of the oxo compound would react, because as bases such compounds are comparable in strength to water. However, such complexes are important from the standpoint of chemical reactivity, for they are believed to be involved in various acid-catalyzed reactions of aldehydes and ketones. The acetone onium ion is stabilized by resonance involving the two forms VIII and IX.





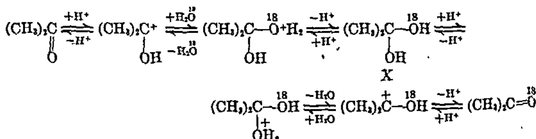
Of these two, IX would be expected to contribute more to the structure of the onium ion than VII (p. 260) does to the structure of acetone. Thus a nucleophilic reagent stable under acid conditions (water or alcohol) could be expected to react more readily with the onium complex than with the uncomplexed compound. Some acid-catalyzed reactions will be presented from this point of view.

6. *Addition of water.* An oxo compound forms a hydrate. The product is a dihydroxy compound, usually unstable. In aqueous solution there is an equilibrium between water, the oxo compound, and the hydrate. Very little formaldehyde in an aqueous solution is present as CH_2O, for the characteristic absorption bands of the ultraviolet spectrum of formaldehyde vapor are not shown by the aqueous solution. Ketones show less tendency to form hydrates than aldehydes. It is significant that $-\Delta H$ of hydrogenation is in the order: $CH_2O > RCHO > R_2CO$ (p. 262); $-\Delta H$ of hydration presumably would be in the same order, and this order would explain the differences in stability of the hydrates.



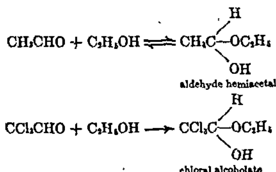
Usually compounds in which two hydroxyl groups are attached to the same carbon atom cannot be isolated, for on heating they decompose to the more volatile components which react to form them. However, when the dihydric compound is a solid and will crystallize from solution, the compound can be isolated. One of the best known aldehyde hydrates is chloral hydrate. Trifluoroacetone, CF_3COCH_3, is one of the few ketones forming a stable hydrate.

Proof that ketones react with water is shown by the exchange of heavy oxygen for oxygen of normal isotopic composition when acetone of normal oxygen content is added to water having a high content of heavy oxygen, $\overset{18}{O}$. The reaction is acid catalyzed.

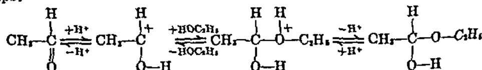


The steps outlined above are believed to represent the way oxygen is exchanged. The hydrate, X, is seen to be an intermediate.

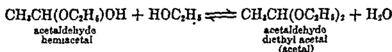
7. *Reaction with alcohols; hemiacetals, acetals, and α-chloroethers.* Aldehydes react reversibly with alcohols under anhydrous conditions and in the presence of an acid catalyst to form hemiacetals (semiacetals). Like the hydrates above, hemiacetals in general are unstable and exist only in solution, for they easily dissociate into the reactants. However, in some cases the hemiacetal is stable enough to be distilled. This is true of acetaldehyde monoethylacetal (aldehyde hemiacetal), which boils at 74 to 85°. In case the hemiacetal is a solid, it may separate from solution. This is true of trichloroacetaldehyde hemiacetal (chloral alcoholate), which is quite stable.



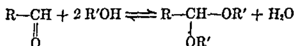
The acid catalyst is believed to promote the reaction through the following steps:



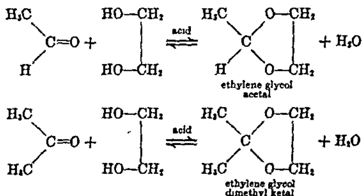
With an excess of alcohol and in the presence of a solid dehydrating agent, usually anhydrous calcium chloride or anhydrous copper sulfate, which is added to absorb the water formed, the final reaction product is an acetal. A hemiacetal is an intermediate, and it reacts reversibly with alcohol to form the acetal.



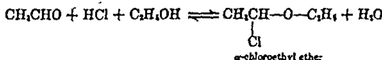
Both the forward and reverse reactions are acid catalyzed. Acetals are stable compounds and distil without decomposition. They do not reduce ammoniacal silver ion. In the preparation of acetals of higher aldehydes, removal of the water formed by azeotropic distillation with benzene or other suitable liquid allows the reaction to proceed.



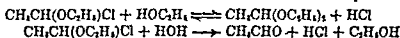
Glycols form cyclic acetals. Glycols even react with ketones to form cyclic ketals.



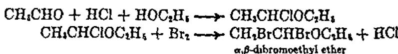
When a mixture of aldehyde (preferably paraldehyde) and alcohol is saturated with dry hydrogen chloride, the main product is an *alpha*-chloroether, resulting from the reaction of both hydrogen chloride and alcohol with the aldehyde.



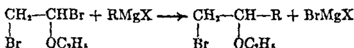
Chloroethers of this type on standing become dark because of decomposition and polymerization. Excess of alcohol, or addition of a metallic alkoxide, converts these chloroethers to acetals; addition of water causes hydrolysis.



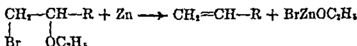
An important method of synthesizing alkenes proceeds through α-chloroethers (Boord synthesis). By the action of bromine the α-chlorine atom and a β-hydrogen atom are replaced by bromine.



With Grignard reagents the α-bromine atom is replaced by an alkyl group. This shows the activating effect of the neighboring ethoxy radical.

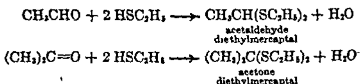


When metallic magnesium is added to the resulting β-bromoether, or when the latter is heated with metallic zinc, the elements of ethyl hypobromite are removed by the metal and an olefin results.



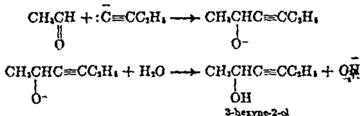
When higher aldehydes replace acetaldehyde, the products are 1,2-dialkylated ethylenes.

8. *Reaction with mercaptans; mercaptals.* Aldehydes and ketones react more readily with thioalcohols (mercaptans) than with alcohols.



The products resemble acetals and are called mercaptals. They are quite stable towards hydrolysis under acid, as well as basic, conditions.

9. *Addition of sodium alkynides.* These strongly nucleophilic reagents add rapidly to aldehydes and ketones to yield sodium salts of unsaturated secondary and tertiary alcohols, respectively. Decomposition with water yields the corresponding alcohol.

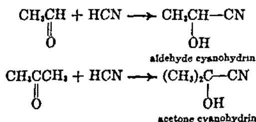


Thus sodium 1-butynide yields 3-hexyne-2-ol with acetaldehyde, and 2-methyl-3-hexyne-2-ol with acetone. As in reactions of these metallic alkynides with carbon dioxide (p. 86), it is the carbanion that reacts with the aldehyde or ketone. It was pointed out (p. 260) that acetone is a resonance hybrid and that in one of the resonance forms VII, the carbon atom is strongly elec-

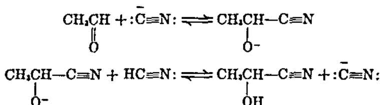
trophilic. The reaction is essentially bond formation between the electrophilic carbon atom of acetone and the nucleophilic carbon atom of the alkynide ion.

10. *Addition of Grignard reagents and other organometallic compounds.* These react similarly to sodium alkynides. The reactions have been described previously (pp. 132, 138). Alkyl lithiums are replacing Grignard reagents to some extent. Aldehydes (except formaldehyde) yield secondary alcohols; ketones, tertiary alcohols; and formaldehyde, primary alcohols. Usually dry paraformaldehyde is used in place of formaldehyde.

11. *Addition of hydrogen cyanide; the cyanohydrin reaction.* Aldehydes and ketones add hydrogen cyanide to form α-hydroxynitriles (cyanohydrins).

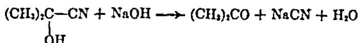


Cyanide ion reacts about 100 times as rapidly as does hydrogen cyanide. When anhydrous hydrogen cyanide is the reagent, either a small amount of sodium or potassium cyanide should be present, or a small amount of a tertiary amine, to furnish cyanide ion. Cyanide ion reacts to form cyanohydrin ion, and this in turn reacts with hydrogen cyanide, yielding the cyanohydrin, and regenerating cyanide ion.

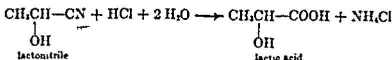


With lower aldehydes and ketones the reaction usually is carried out in aqueous solution, using a metallic cyanide and an acid.

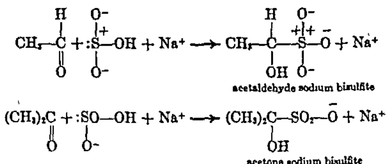
The reactions are reversible, and many systems reach a measurable equilibrium. Aldehydes react more completely than ketones. In 95 per cent alcohol the equilibrium constant is 33 in the reaction of acetone with hydrogen cyanide. The ketone can be regenerated when a ketone cyanohydrin is heated with aqueous base.



When heated with concentrated hydrochloric acid, cyanohydrins are hydrolyzed to *alpha*-hydroxy acids.



12. *Addition of sodium bisulfite.* Acetaldehyde and acetone react readily with aqueous sodium bisulfite to form nonvolatile sodium compounds.

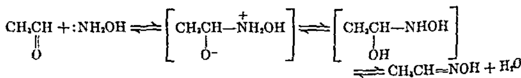


Higher aldehydes and methyl ketones also react, but more slowly. With higher dialkylated acetones, especially the symmetrically substituted ones, the reaction is too slow to be of any practical value. Aqueous-alcoholic bisulfite works better with higher compounds when they are only slightly soluble in aqueous bisulfite.

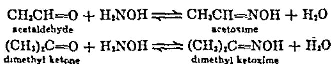
The bisulfite addition compounds of lower aldehydes and ketones are soluble in water, higher ones less soluble. They are largely salted out by excess sodium bisulfite when a saturated solution of the reagent is used. The reaction is useful in purifying an aldehyde or ketone from a compound that does not react. If the latter is readily volatile, it can be removed by steam distillation; if insoluble in water, it can be separated from a dilute aqueous solution of the bisulfite compound; if soluble in water, it remains in solution while the addition compound is caused to crystallize more or less completely by adding an excess of saturated bisulfite solution. Steam distillation, if indicated, should be done rapidly because the reaction is slightly reversible

Heating the bisulfite addition compound with dilute aqueous acid or base (carbonate, if an aldehyde) regenerates the original compound. Thus it may be obtained in a purer condition after the bisulfite compound has been freed of impurities. Crystallization of the bisulfite compound usually is the preferred method of purification.

13. *Reaction with hydroxylamine; oximes.* Aldehydes and ketones react, the former more readily, with hydroxylamine. The first step is believed to be addition to form an unstable intermediate, which by loss of water is converted to the oxime.

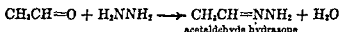


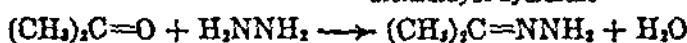
In some cases the first reaction product is stable (see Chloral, p. 285). The overall reaction to form an oxime is a condensation reaction in which water is eliminated.



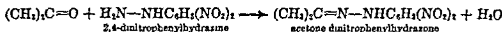
The reactions are acid catalyzed and reversible. The original oxo compound can be recovered by heating with a dilute aqueous strong acid. Thus there is an optimum *p*H for the formation of an oxime, usually that of aqueous acetic acid containing some sodium acetate. The oxime reaction formerly was much used as a test for the oxo group, since oximes are less soluble in aqueous solutions than the original compound, but many of them are liquids at room temperature. Hydrazine and, especially, its organic derivatives are much superior.

14. *Reaction with hydrazine and substituted hydrazines; hydrazones.* Hydrazine reacts in a manner similar to that of hydroxylamine, presumably through an unstable intermediate. The reactions are acid catalyzed, and reversible, as with hydroxylamine.

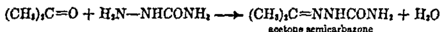




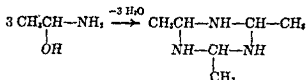
Hydrazones prepared with substituted hydrazines usually are less soluble and have higher melting points. Phenylhydrazine, $C_6H_5NHNH_2$, gives phenylhydrazones. One of the most useful reagents is 2,4-dinitrophenylhydrazine, for all of the hydrazones prepared with this reagent are solids (Chap. 32).



Semicarbazide, $NH_2NHCONH_2$, reacts similarly to hydrazine, and usually more readily. The products, called semicarbazones, are useful derivatives, for the melting points in general are higher than those of the hydrazones.

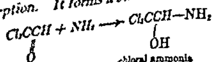


15. *Reaction with ammonia.* Formaldehyde forms urotropin (p. 280). Acetaldehyde and lower homologs rapidly react with gaseous or concentrated aqueous ammonia to form aldehyde ammonias, solid compounds which are somewhat unstable. They are believed to have the general structure of an α-amino alcohol, $RCH(OH)NH_2$. However, molecular weight determinations yield values two and three times the simple formulas. On standing, the product from acetaldehyde ammonia forms a cyclic compound.



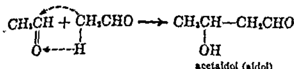
In general, compounds are unstable when amino and hydroxyl groups are attached to the same carbon atom, for ammonia tends to form, with regeneration of the original organic compound. Actually this happens when aldehyde ammonias are heated with dilute mineral acids, as in the case of oximes, etc.

Chloral is an exception. It forms a stable amino alcohol, chloral ammonia.



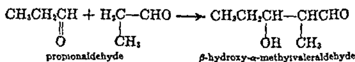
Ketones react readily with ammonia, usually with the production of mixtures *of two or more compounds.* These are formed from two or more molecules *of the first addition products.*

16. *The aldol condensation.* An aldehyde undergoes a reaction which is a type of polymerization, but differs from the usual polymerization of an aldehyde (p. 283) in the formation of a new carbon-to-carbon bond. On this account it is called a condensation reaction. It takes place best under mildly alkaline conditions, for example, sodium bicarbonate, carbonate, or acetate or dilute sodium hydroxide or even an alkoxide in low concentration. Other compounds can promote the reaction, for example, dilute hydrochloric acid.

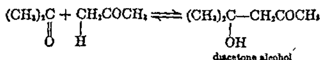


The product, β-hydroxybutyraldehyde, is called aldol (*ald*ehyde-alcoh*ol*). The reaction takes place between the carbonyl carbon atom of one molecule and the *alpha*-carbon atom of another molecule. (The mechanism of the reaction is discussed under enolization, p. 275.) In dilute aqueous solution the reaction reverses to a slight extent. This shows that an equilibrium exists and that at equilibrium only a slight amount of aldehyde is present, except when the solution is highly diluted. If the aldol condensation could take place in the gas phase, ΔH would be -2.5 kcal. per mole of aldol, as calculated from bond energies. Because of the small heat effect an equilibrium system would be expected. However, for closer approximation one should take account of other factors, in particular heats of vaporization and the $T\Delta S$ term of equation 4, page 23.

Higher aldehydes also may condense. The new bond is formed between the carbonyl carbon of one molecule and the *alpha*-carbon atom of the other. Thus β-hydroxy-α-methylvaleraldehyde is formed from propionaldehyde.



Acetone undergoes a similar condensation but at a lower rate. Moreover at equilibrium only a few per cent of the product, 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol) is present.



It is necessary to use a strong base as catalyst. A satisfactory conversion to diacetone alcohol can be realized by adding acetone to concentrated aqueous sodium hydroxide at 0°, when the desired product separates as a second liquid phase, or by recycling acetone, by distillation, onto and through solid barium hydroxide. The concentration of diacetone alcohol in the boiler slowly increases.

In the reaction products above, *viz.*, aldol and diacetone alcohol, the hydroxyl group is in the *beta*-position to the carbonyl group. As in the case of *beta*-hydroxy acids, these undergo dehydration when distilled in the presence of an acidic substance, for example, sodium bisulfate. Thus aldol is converted to crotonic aldehyde and diacetone alcohol to mesityl oxide.

$$\underset{\text{acetaldol}}{CH_3CH(OH)CH_2CHO} \longrightarrow \underset{\text{crotonic aldehyde}}{CH_3CH{=}CHCHO} + H_2O$$

$$\underset{\text{diacetone alcohol}}{(CH_3)_2C(OH)CH_2COCH_3} \longrightarrow \underset{\text{mesityl oxide}}{(CH_3)C{=}CHCOCH_3} + H_2O$$

The reactions are reversible and when either of the products stands in aqueous acid, it is partially reconverted into the respective hydroxy compound.

When acetone is saturated with dry hydrogen chloride and the solution is allowed to stand for some time, both the condensation and dehydration reactions take place. Two products are formed, *viz.*, mesityl oxide and phorone, the latter from three molecules of acetone, through mesityl oxide.

$$\underset{\text{mesityl oxide}}{(CH_3)_2C{=}CHCOCH_3} + O{=}C(CH_3)_2 \longrightarrow \underset{\text{phorone}}{(CH_3)_2C{=}CHCOCH{=}C(CH_3)_2} + H_2O$$

When a mixture of acetone and concentrated sulfuric acid is heated, a hydrocarbon, mesitylene, distils. This, like phorone, results from three molecules of acetone, but the third molecule reacts so as to involve the oxo group of mesityl oxide.

```
         CH3                                   CH3
         |                                     |
    CH—C=[O   H2]CH          —→          CH—C=CH        + 2 H2O
    ||        |                          ||    |
H3C—C—CH[H2  O]=C—CH3              H3C—C—CH=C—CH3
 mesityl oxide    acetone                mesitylene
```

Aldehydes darken when heated with aqueous sodium hydroxide and a dark colored product settles out. This is called aldehyde resin. The reaction can serve as a test for aldehydes. The resin is a mixture of higher-molecular-weight compounds resulting from further condensation reactions involving crotonic aldehyde and higher unsaturated aldehydes. The color is due to the presence of a number of double bonds in the molecule. The reaction of acetaldehyde with crotonaldehyde may proceed in two different ways.

$$CH_3CHO + CH_3CH{=}CHCHO \longrightarrow CH_3CH{=}CHCH{=}CHCHO + H_2O$$

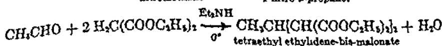
$$CH_3CH{=}CHCHO + CH_3CHO \longrightarrow \underset{\text{sorbic aldehyde}}{CH_3CH{=}CHCH{=}CHCHO} + H_2O$$

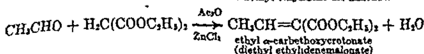
The resemblance in reactivity between the methyl groups of crotonaldehyde and acetaldehyde is explained on the principle of vinylology. These two compounds differ from each other only by the vinylene group, —CH=CH—. It has been observed

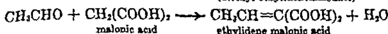
that usually the insertion of the vinylene group between two other functional groups in a molecule allows the effect which one exerts upon the other in the simpler compound still to operate in the vinylog, that is, the one having the vinylene group. Thus the characteristic reactivity of the α-methyl group of acetaldehyde resulting from its proximity to the carbonyl group is shown by the γ-methyl group of crotonaldehyde, whereas it is the α-methylene group of butyraldehyde that reacts.

Nitroparaffins, ethyl malonate, and malonic acid also undergo condensations with aldehydes similar to the aldol condensation. Under basic conditions nitromethane yields 1-nitro-2-propanol. Ethyl malonate yields tetraethyl ethylidene-bis-malonate at 0° with diethyl amine as a catalyst and diethyl ethylidenemalonate, when heated at 50° with acetic anhydride and zinc chloride. Malonic acid yields ethylidene malonic acid or crotonic acid (p. 192).

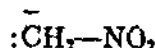
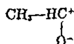








Compounds with which aldehydes condense are customarily regarded as possessing a *labile* hydrogen atom, that is, one that is potentially positive. Under the alkaline conditions it is believed that reaction is initiated by removal of one of the α-hydrogen atoms by the base. The anion resulting from aldehyde is shown as X and the one from nitromethane as XI.

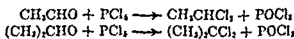
  

X XI XII

Each is thus a nucleophilic reagent, and like an alkynide ion or other similar reagent, becomes attached to the carbonyl carbon atom of aldehyde, reacting as an electrophilic reagent, XII.

It should be noted that the carbanions X and XI are stabilized by resonance. Moreover, since the original compounds have only weakly acidic properties, only a relatively small fraction would be present as carbanions.

17. *Replacement of oxygen by halogens.* Phosphorus pentachloride or pentabromide (phosphorus tribromide and bromine) react to replace an oxygen atom of an aldehyde or ketone by two halogen atoms.



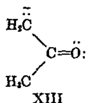
18. *Enolization.* Under vinyl alcohol (p. 165) it was pointed out that acetaldehyde and vinyl alcohol are in equilibrium and that the equilibrium

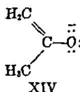
lies very far over on the side of aldehyde, since it is more stable than vinyl alcohol by about 15 kcal., when calculation is made from bond energies. Similarly, a ketone is more stable than the corresponding enol by about 18 kcal.

Addition of a base promotes enolization.

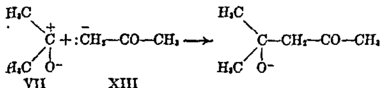


The negative ion is stabilized by resonance involving two forms which in the case of acetone are XIII and XIV. Of these two XIV makes the greater contribution to the structure.

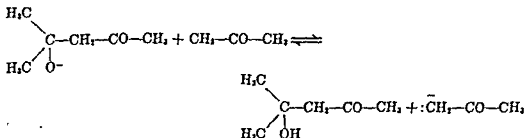




This stabilization of the negative ion makes acetone a stronger acid than it would be otherwise. There is only a small fraction of the ketone in the form of the ion under basic conditions when water is the solvent. The negative ion is believed to be an intermediate in many reactions as, for example, in halogenations and condensations. In the condensation reaction that leads to the formation of diacetone alcohol, the carbanion ion, reacting as XIII, is believed to add to a molecule of acetone, reacting as VII, page 260.



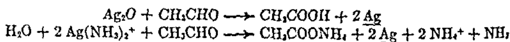
The resulting negative ion of diacetone alcohol reacts with a third molecule of acetone, forming diacetone alcohol and regenerating the negative ion of acetone.



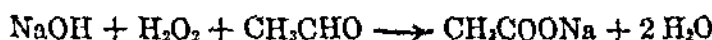
A similar mechanism can be written for the condensation of acetaldehyde to aldol.

19. *Oxidation.* Aldehydes differ from ketones in being more easily oxidized. They are oxidized by silver oxide, ammoniacal silver ion, hot Fehling's

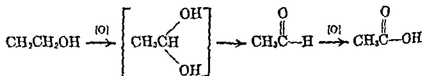
solution (alkaline cupric tartrate), alkaline hydrogen peroxide, and neutral permanganate, reagents that ordinarily do not oxidize ketones.



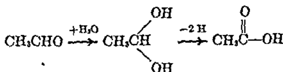
Silver oxide is especially valuable for oxidizing an aldehyde to an acid when the aldehyde is rare, as in structural investigations of rare products. Ammoniacal silver solution or Tollen's solution (ammoniacal silver solution plus sodium carbonate or hydroxide) often produces silver in mirror form. Fehling's solution produces a red precipitate of cuprous oxide. The formation either of metallic silver or of cuprous oxide with the respective reagent often serves as a convenient method of distinguishing an aldehyde from a ketone. Aldehydes sometimes are determined quantitatively by oxidation with hydrogen peroxide in the presence of a known amount of base.



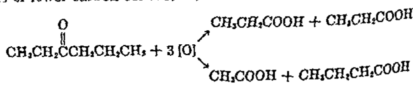
The presence of the hydrogen atom in the CHO group is responsible for the stronger reducing power of an aldehyde as compared to a ketone. The oxidation reaction therefore is a continuation of the oxidation process by which the aldehyde is formed from a primary alcohol. Conveniently it also may be regarded as a process of hydroxylation, *i.e.*, the conversion of a hydrogen atom to the hydroxyl group.



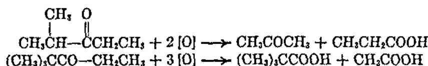
However, experimental evidence indicates that dehydrogenation may be the essential step in the oxidation, rather than hydroxylation. The oxidizing agent is believed to remove hydrogen from the aldehyde hydrate.



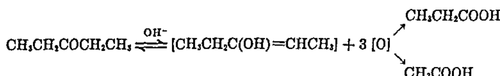
Ketones, although more resistant to oxidation than aldehydes, are attacked by the more powerful oxidizing agents, such as chromic acid in fairly concentrated sulfuric acid and permanganate in alkaline solution (aqueous). In both cases, the carbon chain is broken adjacent to the carbonyl group, yielding acids of lower carbon content.



In general, mixtures of acids are obtained, but as a rule the carbonyl group tends to stay combined with the smaller radical. When one of the radicals is secondary, a ketone and an acid, both of lower carbon content, are the primary oxidation products, and when one radical is tertiary, the carbonyl group stays with it.



When the oxidation is done by alkaline permanganate, formation of the enol is believed to facilitate oxidation by the production of a double bond, at which point the carbon chain is broken.



20. *Simultaneous oxidation and reduction of aldehydes; dismutation* When formaldehyde stands with concentrated sodium hydroxide, sodium formate and methanol are formed. This is sometimes called the **Cannizzaro reaction.** The intermediate oxidation stage to which formaldehyde belongs changes to the more stable acid and alcohol stages by an exothermic reaction.

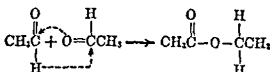


If the dismutation could take place in the absence of alkali, ΔH for the gaseous reaction would be about -26 kcal., according to calculation with bond and resonance energies.



Under alkaline conditions the reaction is even more exothermic.

Aldehydes in which there is an *alpha*-hydrogen atom usually, under alkaline conditions, undergo the aldol condensation rather than dismutation. However, in the alcoholic fermentation of sugar by yeast, an intermediate step is a dismutation of acetaldehyde to alcohol. Other aldehydes also can be reduced to alcohols when added to an actively fermenting yeast culture. A reaction which is closely akin to the Cannizzaro reaction takes place when the proper anhydrous base is added to acetaldehyde. Such a compound is aluminum ethoxide, which promotes the conversion of acetaldehyde to ethyl acetate. The reaction is essentially the transference of a hydrogen atom from one molecule of aldehyde to the other.

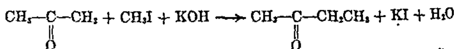


It is believed that an ester is an intermediate in the Cannizzaro reaction, and that this is saponified by the base to yield the alcohol and a salt of the acid.

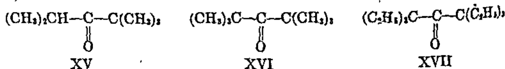
21. *Color with Schiff's reagent.* Aldehydes, but not ketones, produce an intense red color with Schiff's reagent, an almost colorless solution obtained by passing sulfur dioxide into an aqueous solution of the red dye, fuchsine. This is a delicate test for aldehydes. Formaldehyde reacts differently from other aldehydes (p. 262).

22. *Polymerization.* Aliphatic aldehydes, especially the lower ones, polymerize readily. The reaction, promoted by the addition of a trace of strong acid, is described in more detail under formaldehyde and acetaldehyde. Ketones do not form polymers of similar type but may undergo condensations (mesityl oxide, etc.).

23. *Alkylation of ketones.* In the presence of an anhydrous strong base, methyl iodide or ethyl iodide reacts with acetone to yield an α-alkylated product.

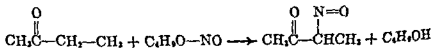


Methyl iodide can react further. By heating to 140°, pentamethylacetone, XV, is formed.

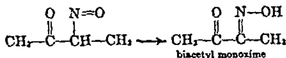


By the use of the stronger base, sodamide, in place of potassium hydroxide, alkylation takes place readily at 80° (in boiling benzene) and yields various products, even hexamethylacetone, XVI. Ethyl iodide also will yield the completely alkylated ketone, hexaethylacetone, XVII. All three of these highly branched ketones are quite unreactive.

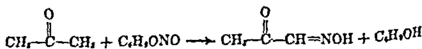
24. *Nitrosation of ketones.* By the action of an alkyl nitrite, for example, butyl nitrite, an *alpha*-nitroso ketone is formed.



The compound is not stable in the nitroso form, for the actual product is an oxime.



Reaction takes place only at an *alpha*-position. Methyl ketones react at a methylene group, rather than at the methyl group. However, acetone also reacts with an alkyl nitrite, yielding methylglyoxal monoxime.



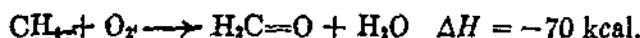
Summary. Aldehydes and ketones are similar in their tendency to react readily with many compounds, for example, sodium alkynides, other organometallic compounds, hydrogen cyanide, hydroxylamine, hydrazine, many derivatives of hydrazine, and sodium bisulfite. Aldehydes undergo the aldol condensation more readily than do ketones; also they differ from ketones in ease of oxidation and in tendency to polymerize. In general, relative reactivities are in the order: formaldehyde > acetaldehyde > other aldehydes > acetone > other methyl ketones > other ketones. Reactivity usually diminishes with increase in the size of the alkyl group but more strikingly with branching of the carbon chain at the *alpha*-position.

Formaldehyde, Methanal, $H_2C{=}O$. Industrially this is produced by partial oxidation of methanol in the gas phase at elevated temperatures (up to 600°) and over a suitable catalyst, usually copper gauze. Many other catalysts have been proposed, mainly heavy metals or metallic oxides or various mixtures of these. Metallic silver and vanadium oxides are especially effective catalysts. Yields are 60 per cent or higher. Because of the exothermic nature of the reaction ($\Delta H = -36$ kcal., from bond energies), the catalyst may reach a temperature of 600°. At this temperature some decomposition of the aldehyde may take place (p. 261).



$$CH_3OH + \tfrac{1}{2}\,O_2 \longrightarrow H_2C{=}O + \tfrac{1}{2}\,H_2O \quad \Delta H = -36 \text{ kcal.}$$

Many methods of obtaining formaldehyde by partial oxidation of methane or of natural gas have been proposed. In general, yields are relatively low, no doubt because of the higher temperature needed for initiating the oxidation, and the more exothermic nature of the oxidation reaction, relative to that of methanol.



$$CH_4 + O_2 \longrightarrow H_2C{=}O + H_2O \quad \Delta H = -70 \text{ kcal.}$$

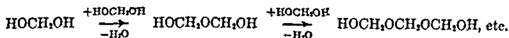
Methane can be converted to formaldehyde through the intermediary of methylene chloride, obtained by chlorination. This undergoes hydrolysis at elevated temperatures (450°) with an effective catalyst (for example, tin phosphate).



$$H_2CCl_2 + H_2O \longrightarrow H_2C{=}O + 2\,HCl$$

Hydrogenation of carbon monoxide is another possible method of manufacture.

Pure formaldehyde is a gas (b.p. −21°). It has a great tendency to polymerize either as a liquid or gas, especially if moisture is present. It is very soluble in water. The commercial solution, formalin, has 40 per cent formaldehyde and 5 to 12 per cent methanol. The latter prevents the deposition of solid paraformaldehyde. Formaldehyde is present largely as methylene glycol (p. 158) and as higher ethers of methylene glycol (more accurately acetals), called **polyoxymethylenes.**



$$HOCH_2OH \xrightarrow[-H_2O]{+HOCH_2OH} HOCH_2OCH_2OH \xrightarrow[-H_2O]{+HOCH_2OH} HOCH_2OCH_2OCH_2OH, \text{ etc.}$$

Efficient fractional distillation of formalin yields a liquid boiling at 99° (56 per cent formaldehyde) which has been claimed to be an azeotropic mixture, 90 per cent methylene glycol, 10 per cent water. When water and methanol are largely removed by evaporation from formalin solution, a white solid, paraformaldehyde, separates and finally remains behind.

Paraformaldehyde is readily soluble in water and when strongly heated decom-

poses to formaldehyde. It is composed of at least four different polymers, which are designated as α, β, γ, and ∂-polyoxymethylenes. They have different molecular weights These depend upon the presence, at the end of the molecule, of a methoxyl instead of a hydroxyl group, which is necessary for continuation of the polymeric reaction.

Reactions of Formaldehyde. This aldehyde is more reactive than other aldehydes (p. 262). It polymerizes readily, condenses readily with other aldehydes, etc., and dismutes easily. The condensation reaction of formaldehyde with itself under mildly basic conditions to form sugars is important. It resembles an aldol condensation but differs from a typical one in not involving an alpha carbon atom.

1. *Reaction with ammonia; hexamethylene tetramine, urotropin.* This is rapidly formed when aqueous ammonia and formaldehyde are mixed.



$$6\,CH_2O + 4\,NH_3 \longrightarrow (CH_2)_6N_4 + 6\,H_2O$$

Urotropin was the first organic compound to have its crystal structure determined by the X-ray method. The structure determined by chemical behavior was confirmed by this method and found to consist of four six-membered rings of alternate carbon and nitrogen atoms (Fig. 13). The measurements showed that not only are the two carbon valences (those holding the nitrogen atoms) at tetrahedral angles to each other, but the three nitrogen valences also make tetrahedral angles with each other. Urotropin is used in medicine, either alone or in combination with other compounds, as a urinary antiseptic.

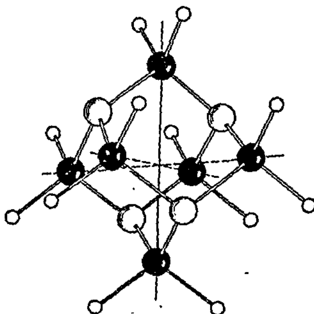
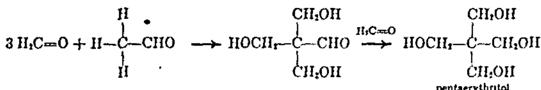


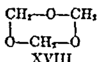
Figure 13 · Structure of Urotropin

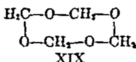
2. *Aldol condensations with other compounds.* Formaldehyde condenses readily with aldehydes and ketones having α-hydrogen atoms. Moreover in some cases, as for example with acetaldehyde, all of the α-hydrogen atoms can react. Actually acetaldehyde reacts with four molecules of formaldehyde, because an intermediate product undergoes reduction to the final product, pentaerythritol, by a "crossed" Cannizzaro reaction.



The hydroxymethyl group, CH_2OH, oftentimes called **methylol**, is produced in a large number of condensations involving formaldehyde. Since it is a primary alcohol group, products resulting from formaldehyde condensations are less subject to unsaturation than those from other aldehydes or from ketones. Formaldehyde condenses readily with nitroparaffins (Chap. 24), urea (Chap. 22), phenols (Chap. 33), and many other substances.

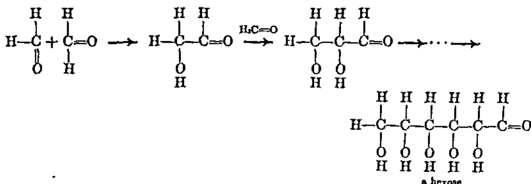
3. *Polymerization*. In addition to paraformaldehyde, other polymerization products of formaldehyde are trioxymethylene, tetraoxymethylene, and "formose" Trioxymethylene, metaformaldehyde (m.p. 61°, b p. 115°), sublimes when paraformaldehyde is heated with dilute sulfuric acid. In the vapor state it has a molecular weight corresponding to a trimer, $(CH_2O)_3$. Unlike formaldehyde it does not readily reduce silver ion. These properties are in keeping with structure XVIII, which is a cyclic acetal.





Tetraoxymethylene, XIX, is a cyclic acetal also. It is obtained by pyrolysis of polyoxymethylene diacetate.

An important condensation of formaldehyde takes place under mildly basic conditions. Dilute formaldehyde, to which some calcium hydroxide has been added, after standing for some time yields a complex mixture of sugarlike compounds, called **formose**, mainly pentoses, $C_5H_{10}O_5$, and hexoses, $C_6H_{12}O_6$ (Chap. 42). These are believed to result from successive additions of formaldehyde.

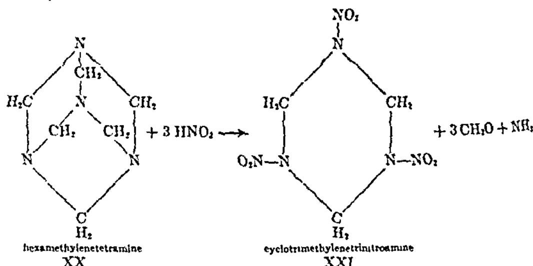


From the mixture the phenylhydrazone of inactive fructose, $C_6H_{12}O_6$, was isolated by Emil Fischer. The formation of sugars from formaldehyde was thought, in the past, to be one of the steps involved in the biochemical synthesis of sugars from carbon dioxide in the green leaves of plants This possibility intrigued chemists for decades. It is now known that formaldehyde is not an intermediate in photosynthesis.

Uses of Formaldehyde. Formaldehyde is a powerful germicide and antiseptic, a property resulting from its ready reactivity with protein, and thus with protoplasm,

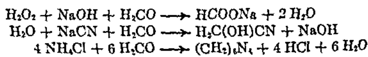
a constituent of all living cells It finds wide application in disinfecting, sterilizing, and embalming. It hardens protein, and thus is used as a tanning agent, also for the production of plastic substances from gelatin, albumin, and other protein material. The most extensive application of formaldehyde now is in the manufacture of synthetic plastics, as for example "Bakelite," from formaldehyde and phenol (Chap. 33), and "Betel ware," from formaldehyde and urea (Chap. 22).

Hexamethylene tetramine, XX (also Fig. 13, p 280), besides its value in medicine, is an important industrial product. It is an accelerator for the vulcanization of rubber and is much used in the plastics industry, especially in combination with phenols, and from it the valuable explosive, cyclonite, XXI, is obtained by the action of 100 per cent nitric acid.



Paraformaldehyde is used in fumigation. It may be heated, to cause decomposition to formaldehyde vapor, or it may be mixed with solid potassium permanganate. Oxidation of a part generates sufficient heat to decompose much of the remainder.

Detection and Estimation of Formaldehyde. A number of color tests have been developed for the detection of formaldehyde. With Schiff's reagent the intense color is purplish, rather than red, as with most other aldehydes, and moreover the color is not discharged on the addition of sulfuric or phosphoric acid. Formaldehyde may be quantitatively estimated colorimetrically by comparing the depth of color with known color standards. Other quantitative methods are: oxidation to formic acid by means of hydrogen peroxide in the presence of excess standard base, reaction with an excess of standard sodium cyanide, and reaction with aqueous neutral ammonium chloride.



$$H_2O_2 + NaOH + H_2CO \longrightarrow HCOONa + 2\,H_2O$$
$$H_2O + NaCN + H_2CO \longrightarrow H_2C(OH)CN + NaOH$$
$$4\,NH_4Cl + 6\,H_2CO \longrightarrow (CH_2)_6N_4 + 4\,HCl + 6\,H_2O$$

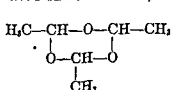
In the first case the excess of base is titrated, in the second the base formed is titrated, and in the third the acid formed is titrated.

Acetaldehyde, Ethanal, CH_3CHO. This is commonly called aldehyde It usually is present in alcohol in small amount as a result of slow oxidation of alcohol by air. In the laboratory it can be prepared by oxidation of alcohol by "chromic acid mixture," more conveniently by depolymerization of paraldehyde (p. 257). Indus-

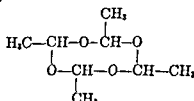
trially the hydration of acetylene is an important process (p. 84), for it is a step in the production of paraldehyde, metaldehyde, acetic acid, ethyl acetate, and other compounds.

Aldehyde has a stupefying odor, but in very dilute concentrations has a fruitlike odor. It occurs in the skin of some fruits, especially apples. It is present also in wines. Part of the aging process of wines is the development of acetallike compounds between aldehyde and hydroxy compounds.

Polymerization of aldehyde takes place readily on the addition of a small amount of strong acid as, for example, sulfuric, perchloric, or toluenesulfonic acid. At room temperature the liquid trimer, **paraldehyde**, is formed. At temperatures below 0° the solid tetramer, **metaldehyde**, can be obtained by the addition of a small amount of a strong acid. The polymerization may take place also under weakly acidic conditions, as with sulfur dioxide. Even calcium chloride may cause the reaction. Since these polymers are not strong reducing agents like aldehyde, it is evident that an aldehyde group is not present in the molecule. Actually they are cyclic acetals, having structures XXII and XXIII, respectively.

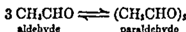


paraldehyde
trimethyltrioxymethylene
XXII



metaldehyde
tetramethyltetraoxymethylene
XXIII

These polymers undergo depolymerization when heated with a small amount of strong acid. This is because, in the presence of the acid, an equilibrium exists, and this is disturbed by the continual removal of the more volatile monomer.



$$3\ CH_3CHO \rightleftharpoons (CH_3CHO)_3$$

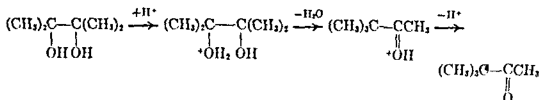
aldehyde — paraldehyde

In this way the polymer is largely converted to monomer, even though equilibrium conditions favor the polymer. The exothermic nature of the polymerization reaction is shown by the rapid boiling of aldehyde when a small amount of 80 per cent sulfuric acid is added.

Paraldehyde produces sleep when taken internally, but is now largely displaced by other hypnotics that do not possess a disagreeable taste and produce a more controlled lasting effect. Metaldehyde, or "meta," is poisonous to slugs and snails, and has the additional advantage that poison bait of which it is an ingredient is rendered more attractive to these pests.

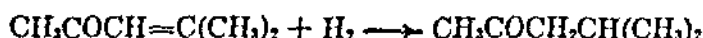
Higher Aldehydes. These are relatively unimportant. **Enanthaldehyde, *n*-heptaldehyde,** $CH_3(CH_2)_5CHO$, is easily obtainable by heating castor oil under reduced pressure until decomposition sets in. **Caprylaldehyde,** $CH_3(CH_2)_6CHO$, and **pelargonaldehyde,** $CH_3(CH_2)_7CHO$, occur in some essential oils, for example, oil of citronella and oil of rose. The last two and many other higher aldehydes possess agreeable odors and are used in perfumery.

Acetone, Propanone, Dimethyl Ketone, $(CH_3)_2CO$. This volatile liquid, b.p. 56°, is completely miscible with water, on the one hand, and with many hydrocarbon liquids, for example, gasoline, on the other. These solubility relationshi



It is believed that as the oxonium compound first formed loses a molecule of water a methyl group migrates. Many other pinacols, *i.e.*, ditertiary glycols, undergo similar changes, which are classified under the title of **pinacol rearrangement**. Sometimes secondary glycols as well undergo rearrangement in the presence of acids, although not so readily as pinacols

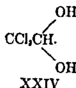
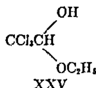
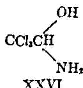
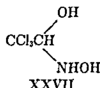
Higher Ketones. Methylisobutyl ketone is an industrial solvent. It is obtained by hydrogenation of *mesityl oxide*.



Some ketones occur naturally, for example, 2-heptanone in Roquefort cheese and 2-nonanone, 2-decanone, and 2-undecanone in oil of rue, which is largely 2-undecanone.

Chloral, Trichloroacetaldehyde, CCl_3CHO. This is the most important halogenated aldehyde, from both a chemical and pharmaceutical point of view. It is prepared from ethyl alcohol by the action of chlorine, which brings about oxidation as well as chlorination.

Chloral reacts rapidly with water, alcohol, ammonia, hydroxylamine, and many other compounds, to form in most cases stable addition products, for example, chloral hydrate, XXIV, chloral alcoholate, XXV, chloral ammonia, XXVI, and chloral hydroxylamine, XXVII.

The presence of the three negative chlorine atoms on the α-carbon atom greatly increases the stability of addition compounds of the above types. The fact that they are solids makes their preparation relatively easy.

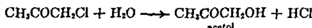
When heated with aqueous alkali, chloral is cleaved to chloroform and a formate.



This is an important step in the haloform reaction (p. 262).

Chloral hydrate when taken internally in small doses induces sleep and in large doses produces complete narcosis It is the effective agent in so-called "knockout drops."

Chloroacetone, CH_3COCH_2Cl. The preparation is described earlier (p. 261). The compound is a lachrymator. It readily undergoes hydrolysis to acetol.



DIOXO COMPOUNDS

The important compounds of this group are classified as α, β, or γ dialdehydes or diketones, or respectively 1,2-, 1,3-, or 1,4-, to indicate the relative

rather unique. On this account acetone is an excellent solvent This is its main value in industry in connection with resins, varnishes, synthetic plastics, and especially cellulose nitrate.

Formerly acetone was obtained exclusively from wood as a by-product of charcoal production. It is a component of pyroligneous acid (p. 150). As a result of the greatly increased demand for acetone during World War I, mainly because of its use as a plasticizer and solvent for nitrocellulose, new methods were developed, because the older source was inadequate to meet the enormous needs. One is the continuous catalytic process from acetic acid, by passing it over a heated metallic carbonate or oxide. The other is the fermentation of starch with *Clostridium acetobutylicum* (p. 153). These last two, along with other fermentations (*Bacillus granulobacter*, on grains), and production from 2-propanol, mainly by dehydrogenation, are important sources of industrial acetone.

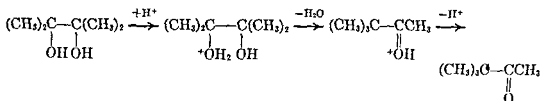
TABLE 59 | Some Miscellaneous Compounds

	M.P. °C	B P °C	SP. GR. 20°/4°	SOLUBILITY IN H_2O G /100 G. 20°
Acrolein	−87.7	52 4	0.841	27
Aldol		83 [a]	1.103	misc.
Chloral	−57	97.7	1.51	react
Chloral hydrate	51.7	96 3	1 619 [b]	780 [c]
Crotonic aldehyde	−69	104.0	0.848	18
Glycolic aldehyde	76		1.46	react.
Glyoxal [d]	15	50	1.366	react.
Methylglyoxal [e]		72 [f]		react.
Paraldehyde	12 55	123.7	0 994	12 [g]
Chloroacetone	−44	119 7	1.170	misc.
Diacetone alcohol	−47	169	0.94	misc.
Dimethylglyoxal [h]		89–90	0.98	25 [i]
Dimethylglyoxime	245–246			0 06
Mesityl oxide	41.5	131.4	0.858	2.8
Methyl isobutyl ketone	−84.7	115 8	0 801	2.0
Phorone [j]	28	198 2	0 883	1?
Pinacolone	−52.5	106.3	0.811	2.5
Carbon suboxide	−107	6.8		react.
Ketene	−151	−56		react.

[a] At 20 mm. [b] At 50°. [c] At 23 7°. [d] Liquid is yellow, vapor, green [e] Yellow. [f] Slowly polymerizes. [g] At 13°. [h] Vapor and liquid both yellow green. [i] At 15°. [j] Yellow.

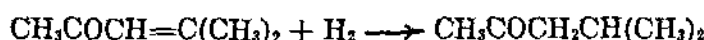
Methyl Ethyl Ketone, Butanone, $CH_3COC_2H_5$. This is an important industrial solvent, for it greatly resembles acetone in this respect, and has the advantage over acetone of less volatility (b.p. 79°). It is produced mainly by dehydrogenation of 2-butanol over a suitable metallic catalyst (copper, copper alloys, etc).

Pinacolone, 3,3-Dimethyl-2-butanone, $(CH_3)_3CCOCH_3$. This formerly was called pinacoline. It is formed from pinacol (p. 263) by an intramolecular rearrangement when it is heated with a dilute, strong acid.



It is believed that as the oxonium compound first formed loses a molecule of water a methyl group migrates. Many other pinacols, i.e., ditertiary glycols, undergo similar changes, which are classified under the title of **pinacol rearrangement.** Sometimes secondary glycols as well undergo rearrangement in the presence of acids, although not so readily as pinacols.

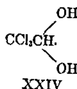
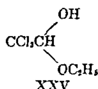
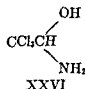
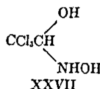
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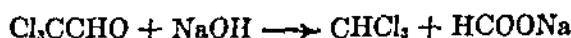
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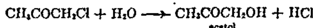
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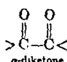
Chloroacetone, CH_3COCH_2Cl. The preparation is described earlier (p. 261). The compound is a lachrymator. It readily undergoes hydrolysis to acetol.

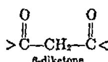


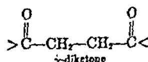
DIOXO COMPOUNDS

The important compounds of this group are classified as α, β, or γ dialdehydes or diketones, or respectively 1,2-, 1,3-, or 1,4-, to indicate the relative

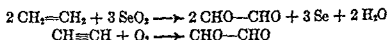
positions of the two functional groups. The designations are applied to diketones more than to other compounds.


α-diketone


β-diketone

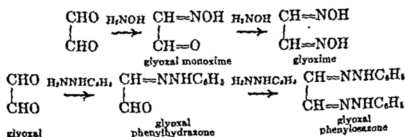

γ-diketone

Glyoxal, CHO—CHO. This is the simplest dialdehyde. It is formed by oxidation of glycol, acetaldehyde, or ethyl alcohol with nitric acid, by oxidation of ethylene with selenium dioxide at temperatures of 110 to 240°, or by a gas phase oxidation of acetylene with oxygen in the presence of nitric oxide.



Because of the great tendency of glyoxal to polymerize (true of other dialdehydes also), it is obtained as the solid polyglyoxal, which on distillation decomposes to a green, pungent gas, monomeric glyoxal. The yellowish liquid obtained on cooling soon polymerizes.

Glyoxal shows the usual typical aldehyde reactions. It reacts with one or two molecules of hydroxylamine, hydrazine, phenylhydrazine, etc.

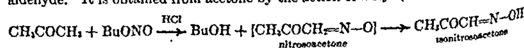


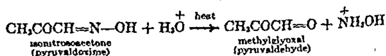
The dioxime usually is called glyoxime and the dihydrazone is called an osazone, a name given to 1,2-dihydrazones.

Under alkaline conditions glyoxal undergoes the Cannizzaro reaction, yielding glycolic acid.

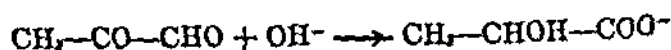


Methylglyoxal, Pyruvic Aldehyde, $CH_3CO—CHO$. This is the simplest ketonic aldehyde. It is obtained from acetone by the action of butyl (or amyl) nitrite.





The stable product, isonitrosoacetone, when heated with aqueous sulfuric acid, is hydrolyzed to methylglyoxal and hydroxylamine sulfate. With alkali, methylglyoxal undergoes dismutation to a salt of lactic acid.

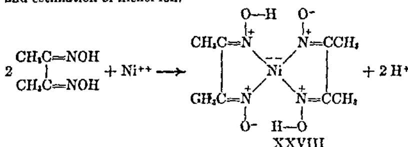


Dimethylglyoxal, Biacetyl, 2,3-Butanedione, $CH_3COCOCH_3$. The older name of diacetyl is being supplanted by biacetyl (the prefix "bi" is preferred when a name is composed of two like radicals). It is found in many essential oils, for example, oil of clove and oil of caraway, and also in butter, of which it is the main odoriferous principle. Biacetyl is easily prepared from methylethyl ketone by the action of an alkyl nitrite.



$$CH_3COCH_2CH_3 \xrightarrow{BuONO} CH_3COC(CH_3){=}NOH \xrightarrow{H_3O^+} CH_3COCOCH_3$$

The product is a yellow oil, b.p. 88°, having the characteristic reactions of ketones. The best known derivative is the dioxime, dimethyl glyoxime. This forms a characteristic, insoluble, red nickel salt, nickel dimethylglyoxime, XXVIII, of value in the detection and estimation of nickel ion.



XXVIII

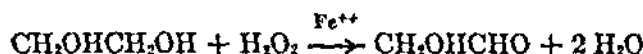
The product is a complex coordination compound between one nickelous ion and two molecules of the oxime, with the nickel atom having a coordination number of four, and forming coordination bonds with four nitrogen atoms. Other metallic ions give colored compounds with this dioxime. The dioximes of glyoxal and methylglyoxal also form many colored complexes with metals, but dimethylglyoxime is the most important of these, owing to ease of preparation.

Acetylacetone, $CH_3COCH_2COCH_3$ is the simplest β-diketone. It is a colorless liquid, b p. 139°. It is described in connection with ethyl acetoacetate (p. 328).

HYDROXY ALDEHYDES AND KETONES

The most important compounds of this group are the sugars, described in Chapter 42. One functional group influences the other to some extent. The relative position of the two groups is important, as shown by the tendency of β-hydroxy compounds to become unsaturated.

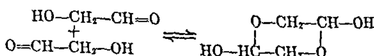
Glycolic Aldehyde, $HOCH_2CHO$. This may be obtained by the oxidation of glycol with hydrogen peroxide in the presence of ferrous salts.



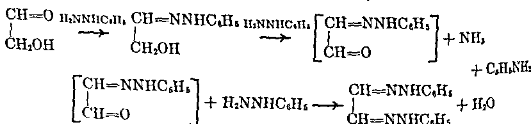
$$CH_2OHCH_2OH + H_2O_2 \xrightarrow{Fe^{++}} CH_2OHCHO + 2\,H_2O$$

It has been detected in the solution resulting from the polymerization of formaldehyde in aqueous solution induced by calcium carbonate. It, therefore, would seem to be the initial product in the formation of hexose sugars from formaldehyde, for it in turn gives hexose sugars under mildly alkaline conditions.

Glycolic aldehyde is a solid and possesses a sweet taste. When first dissolved in water the molecular weight corresponds to that of a dimer, which gradually dissociates to a monomer. The structure is believed to be that of a cyclic hemiacetal.



When heated with phenylhydrazine, glycolic aldehyde yields glyoxal phenylosazone (p. 286) The hydrazone first formed is oxidized by a second molecule of phenylhydrazine, the resulting intermediate product (not isolated) reacts with a third molecule.



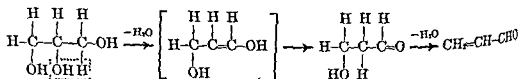
This is a characteristic behavior of α-hydroxy aldehydes and α-hydroxy ketones.

Aldol, β-Hydroxybutyraldehyde, $CH_3CHOHCH_2CHO$, and Diacetone Alcohol, 4-Hydroxy-4-methyl-2-pentanone, $(CH_3)_2C(OH)CH_2COCH_3$. The formation of these in an aldol condensation from aldehyde and acetone, respectively, has been mentioned previously (p. 272). Like β-hydroxy aldehydes and ketones in general, these easily lose water when heated to form unsaturated compounds, in these cases crotonic aldehyde and mesityl oxide, respectively.

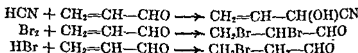
UNSATURATED ALDEHYDES AND KETONES

Acrolein, Acrylic Aldehyde, $CH_2{=}CHCHO$. This is a volatile liquid of suffocating odor. It causes a copious flow of tears and was used during World War I as a lachrymator.

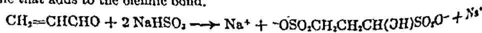
Acrolein is formed when fats are strongly heated; it results from the decomposition of the glyceryl radical at the high temperature. Acrolein is prepared by heating glycerol with potassium bisulfate, which acts catalytically to promote removal of water.



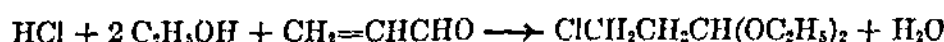
Acrolein shows the reactions of an aldehyde in reducing ammoniacal silver and hot Fehling's solution and in undergoing the cyanohydrin reaction. It reacts like many other unsaturated compounds in adding bromine and hydrogen bromide.



In the last reaction, addition is contrary to Markownikoff's rule, as in the case of α-unsaturated acids. The ability of acrolein to add two molecules of sodium bisulfite shows that the olefinic double bond is more reactive here than in hydrocarbons. Hydrolysis removes the molecule of bisulfite that adds to the carbonyl bond but not the one that adds to the olefinic bond.



An interesting reaction of acrolein is simultaneous acetal formation and addition to the double bond; thus with alcoholic hydrogen chloride the product is β-chloropropionaldehyde diethyl acetal.



$$HCl + 2\,C_2H_5OH + CH_2{=}CHCHO \longrightarrow ClCH_2CH_2CH(OC_2H_5)_2 + H_2O$$

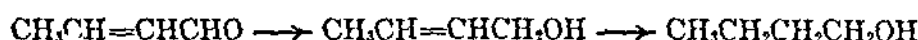
This is a relatively stable compound, which when heated with a base is converted into acrolein acetal.



$$KOH + ClCH_2CH_2CH(OC_2H_5)_2 \longrightarrow CH_2{=}CHCH(OC_2H_5)_2 + KCl + H_2O$$

Polymerization is the most characteristic property of acrolein, and this takes place with extreme ease. Under the proper conditions resins having useful properties can be obtained. The reaction is promoted by oxygen and can be greatly retarded by the addition of a suitable stabilizer which generally is an **antioxidant,** that is, one that reacts readily with organic peroxides. The peroxide is the initial product formed with oxygen and promotes polymerization. Hydroquinone is a commonly used antioxidant.

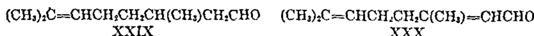
Crotonic Aldehyde, $CH_3CH{=}CHCHO$. The preparation of this has already been described (p. 273). It can be reduced either to crotyl alcohol or to *n*-butyl alcohol.



$$CH_3CH{=}CHCHO \longrightarrow CH_3CH{=}CHCH_2OH \longrightarrow CH_3CH_2CH_2CH_2OH$$

Formerly, before the development of fermentation processes (p. 153), 1-butanol was produced in this way, starting with acetaldehyde.

Citronellal, 3,7-Dimethyl-6-octenal (XXIX) and **Citral, 3,7-Dimethyl-2,6-octadienal** (XXX) The first of these is found in oil of citronella and oil of rose, the second in lemon grass oil and in oil of lemon.



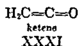
$$\underset{\text{XXIX}}{(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)CH_2CHO} \qquad \underset{\text{XXX}}{(CH_3)_2C{=}CHCH_2CH_2C(CH_3){=}CHCHO}$$

They are mentioned also under terpenes (Chap. 43).

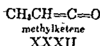
Identification of Aldehydes and Ketones. A generally useful reagent is 2,4-dinitrophenylhydrazine, which in a saturated solution in glacial acetic acid or in alcohol containing hydrochloric acid, gives a solid 2,4-dinitrophenylhydrazone with all but highly branched ketones. Aldehydes give red cuprous oxide with hot Fehling's solution, metallic silver with ammoniacal silver ion, and a color with fuchsin bisulfite (Schiff's reagent).

KETENES

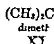
Ketenes are compounds in which a carbonyl group is attached to an unsaturated carbon atom. The simplest member is called ketene. Homologs are isomeric with unsaturated aldehydes or ketones, $C_nH_{2n-2}O$ They are called aldoketenes if there is an *alpha*-hydrogen atom, and k[...]es if there is none. Thus XXXI and XXXII are aldoketenes, and [...] ketoketene.



$H_2C{=}C{=}O$
ketene
XXXI



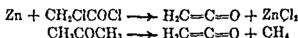
$CH_3CH{=}C{=}O$
methylketene
XXXII



$(CH_3)_2C$
dimeth
XX

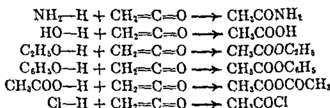
Ketenes are very reactive substances. Each of the molecules above contains a cumulated system of double bonds. Such systems are highly reactive, because of the high energy content (see p. 88). The reactions typical of these compounds are shown by the simplest member, ketene.

Ketene, $H_2C{=}C{=}O$. This is a poisonous gas of suffocating odor. When liquefied it boils at $-56°$. It is prepared from chloroacetyl chloride by passing it over hot metallic zinc or, more conveniently, from acetone by allowing the vapor to come in contact with a red hot platinum wire.



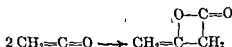
$$Zn + CH_2ClCOCl \longrightarrow H_2C{=}C{=}O + ZnCl_2$$
$$CH_3COCH_3 \longrightarrow H_2C{=}C{=}O + CH_4$$

Ketene reacts with numerous compounds having active hydrogen, *for example*, ammonia, water, alcohols (phenols), and acids, yielding, respectively, acetamide, acetic acid, esters (from alcohols and phenols), and anhydrides (or acyl halides). The reactions may be written as addition to either the olefinic or carbonyl double bond. If the latter is the correct mechanism, then the intermediate enolic type compound rearranges to the final stable product.

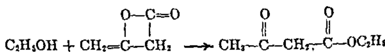


$$NH_2{-}H + CH_2{=}C{=}O \longrightarrow CH_3CONH_2$$
$$HO{-}H + CH_2{=}C{=}O \longrightarrow CH_3COOH$$
$$C_2H_5O{-}H + CH_2{=}C{=}O \longrightarrow CH_3COOC_2H_5$$
$$C_6H_5O{-}H + CH_2{=}C{=}O \longrightarrow CH_3COOC_6H_5$$
$$CH_3COO{-}H + CH_2{=}C{=}O \longrightarrow CH_3COOCOCH_3$$
$$Cl{-}H + CH_2{=}C{=}O \longrightarrow CH_3COCl$$

Ketene often serves as an acetylating agent for alcoholic hydroxyl groups. The results sometimes are complicated by the fact that ketene *readily dimerizes* to ketene dimer, the structure of which has been under dispute for many years, and still is not settled definitely. The one shown below is preferred.

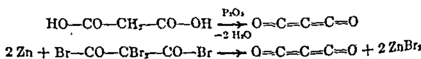


Ketene dimer also reacts readily with compounds having labile hydrogen. With alcohol, for example, ethyl acetoacetate is formed.



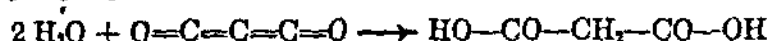
This reaction is the basis of an industrial process for the production of ethyl acetoacetate.

Carbon Suboxide, C_3O_2. This is obtained from malonic acid by heating with phosphorus pentoxide to about 150° under reduced pressure, or from dibromomalonyl dibromide by the action of metallic zinc.



$$HO{-}CO{-}CH_2{-}CO{-}OH \xrightarrow[-2\,H_2O]{P_2O_5} O{=}C{=}C{=}C{=}O$$
$$2\,Zn + Br{-}CO{-}CBr_2{-}CO{-}Br \longrightarrow O{=}C{=}C{=}C{=}O + 2\,ZnBr_2$$

Carbon suboxide is a poisonous gas, b.p. 7°. It is a powerful lachrymator. It is a highly reactive substance, resembling ketene in the type of reactions it undergoes. It reacts very rapidly with water to form malonic acid.



$$2\,H_2O + O{=}C{=}C{=}C{=}O \longrightarrow HO{-}CO{-}CH_2{-}CO{-}OH$$

PROBLEMS

1. Outline a practical laboratory preparation of hexanal in which use is made of the following reaction or reagent:

a) ozonolysis
b) oxidation
c) hydrolysis
d) decarboxylation
e) Grignard reagent
f) reduction

2. Write balanced equations showing how isovaleraldehyde may be prepared in a practical laboratory preparation from the following, using any desired reagents:

a) isoamyl alcohol
b) isobutyl alcohol
c) isopropyl alcohol
d) acetone
e) ethyl alcohol
f) isovaleric acid
g) isovaleronitrile
h) 2,5-dimethyl-3,4-hexanediol
i) 2,5-dimethyl-3-hexene
j) ethyl orthoformate

3. Outline a preparation of 3-pentanone from a compound or compounds of fewer carbon atoms in which use is made of the following reaction or reagent:

a) oxidation
b) decarboxylation
c) hydration
d) acyl halide
e) nitrile synthesis
f) Grignard reagent
g) sodium alkynide
h) zinc compound

4. Outline a practical laboratory preparation of 3-hexanone, starting with the following as the only organic compound or compounds:

a) 3-hexanol
b) 3-hexyne
c) 3-hexene
d) 1-propanol
e) acetylene
f) propionic acid (+ one other org. compd.)
g) *n*-butyric acid (+ one other org. compd.)
h) ethylacetylene (+ one other org. compd.)
i) ethyl cyanide (+ one other org. compd.)
j) *n*-propyl cyanide (+ one other org. compd.)

5. Having acetylene as the only organic compound, and without making use of organolithium or organomagnesium compounds, show steps involved (including reagents) in a synthesis of.

a) acetaldehyde
b) aldol
c) crotonic aldehyde
d) acetone
e) diacetone alcohol
f) 2,4-hexadienal
g) *n*-butyric acid
h) 1-butanol
i) 1-hexanol
j) hexanoic acid
k) mesityl oxide
l) chloroform
m) bromoform
n) ethyl orthoformate
o) 1,1-diethoxybutane
p) 1,1-di-*n*-butoxyethane
q) 2-butanone
r) 3-hexene
s) propanal
t) 4-heptanone
u) 3-hexanone
v) 1-butyne-3-ol
w) 3-methyl-1-butyne-3-ol
x) 2-methyl-3-hexyne-2-ol
y) α-hydroxy-*n*-valeric acid
z) 2-hexanone

6. Show how the Grignard reagent can be applied to the synthesis of the following, starting with one or two compounds of problem 5. Also, show how the starting material may be synthesized from acetylene.

a) 2-hexanol
b) 3-hexanol
c) 2-octanol
d) 2-methyl-2-butanol
e) 3-methyl-3-pentanol
f) [illegible]-2-pentanol
g) 3-ethyl-2-hexanol
h) 3-ethyl-3-hexanol
i) 3-methyl-3-heptanol
j) 3,4-dimethyl-3-hexanol
k) 3,3-dimethylpentane
l) 1,1-diethoxypentane

7. [illegible] possible isomeric (including [illegible]) and indicate which, if any, are unstable.

a) C_4H_8O
b) C_4H_8O
c) $C_4H_8O_2$
d) $C_4H_6O_2$
e) $C_5H_{10}O$ (normal carbon chain)
f) $C_5H_{10}O$ (branched carbon chain)
g) C_5H_8O (normal carbon chain)
h) C_5H_8O (branched carbon chain)

8. Starting with butanal as the only organic compound, show the steps involved in obtaining:

a) 4-heptanone
b) pentanal
c) 1,1-di-n-butoxybutane
d) 1-chloro-1-n-butoxybutane
e) butanaldoxime
f) 2-ethyl-2-hexenal
g) α-hydroxy-n-valeric acid
h) 4-octanone
i) 4-n-propyl-4-octanol
j) 4-n-butyl-4-octanol
k) n-butyl ethylmalonate
l) 3-octyne

9. Show how to synthesize the following, starting with formaldehyde, propionaldehyde, and methyl ethyl ketone as the only organic compounds:

a) α,α-dimethylolpropionaldehyde
b) α-hydroxy-n-butyric acid
c) 3-pentanone
d) 1,1-di-n-propoxypropane
e) 2,3-pentanedione
f) 2,4-dimethyl-3-pentanone
g) α-hydroxy-α-methyl-n-butyric acid
h) 3-hexanol
i) 3-methyl-3-hexanol
j) α-hydroxy-α-ethylbutyric acid
k) 2-methyl-3-hydroxypentanal
l) 2-methyl-2-pentenoic acid

10. Describe a convenient chemical test, stating reagent, conditions, solvent if any, and readily detectable change, that serves to differentiate between:

a) formaldehyde and [illegible]
b) [illegible]
c) [illegible]
d) formaldehyde and [illegible]
e) [illegible]
f) [illegible]
g) acetaldehyde and biacetyl
h) acetaldehyde and acrolein
i) acetaldehyde and trichloroacetaldehyde
j) acetaldehyde and aldol
k) propionaldehyde and acetone
l) n-butyraldehyde and butanone
m) butanone and 3-pentanone
n) 2-pentanone and 3-pentanone
o) n-butyraldehyde and aldol
p) propionaldehyde and acrolein
q) n-butyraldehyde and crotonaldehyde
r) propionaldehyde and pyruvaldehyde

11. Write the formulas of the theoretical oxidation products having the same number of carbon atoms as the following and without initiating oxidation at any other carbon atom

a) propylene glycol
b) 1,2-butanediol
c) 1,3-butanediol
d) 1,4-butanediol
e) 2,3-butanediol
f) 2-methyl-1,2-propanediol
g) 1,4-pentanediol
h) 1,5-pentanediol
i) 1,2,3-butanetriol
j) 1,2,4-butanetriol

12. Show how to synthesize the following by means of the Boord synthesis:

a) 1-pentene
b) 1-hexene
c) 2-pentene
d) 2-hexene
e) 4-methyl-2-pentene
f) 3-methyl-2-pentene
g) 2-methyl-2-pentene
h) 2-methyl-2-butene
i) 3-hexene
j) 2-methyl-3-hexene

13. Describe a procedure by which one component of the mixture below may be recovered, essentially quantitatively and essentially free of the other.

a) acetone and cyclopentane
b) acetone and chloroform
c) acetone and methanol
d) acetone and glycol
e) acetone and methyl acetate
f) butanone and cyclohexane
g) butanone and *n*-butyl chloride
h) butanone and ethanol
i) butanone and ethyl acetate
j) 2-pentanone and formic acid
k) 3-pentanone and acetic acid
l) 4-heptanone and propionic acid

14. Compound *A*, a liquid sparingly soluble in water, gives a solid, *B*, with 2,4-dinitrophenylhydrazine in hot glacial acetic acid. *A* does not give a precipitate with ammoniacal silver nitrate. With hydrocyanic acid it is converted to compound *C*, and this when heated with hydrochloric acid for some time yields compound *D*, α-hydroxy-α-methyl-*n*-valeric acid. Write formulas for *A*, B, and *C*.

15. Compound *A*, $C_8H_{16}O_2$ reduces Tollen's solution, and from the reaction mixture compound *B*, $C_8H_{18}O_2$, can be isolated. This does not reduce Tollen's solution. It does not reduce permanganate ion, either neutral, moderately acidic, or moderately basic. On distillation of *B* at atmospheric pressure compound *C*, $C_8H_8O_2$, is obtained. This does not reduce Tollen's solution. It very rapidly reduces permanganate ion under neutral, acidic, or basic conditions. What deductions can be drawn from these statements? Show how they lead to a possible structure for *A*.

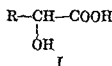
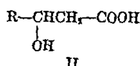
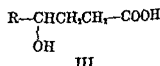
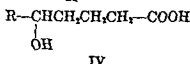
16. Compound *A*, a liquid insoluble in water, gives an intense color with Schiff's reagent and a solid, *B*, when heated with 2,4-dinitrophenylhydrazine in glacial acetic acid. With hydrocyanic acid, *A* yields compound *C*, and this when heated with hydrochloric acid yields compound *D*, α-hydroxy,β,γ-dimethylvaleric acid. Show how a structure for *A* can be deduced from these statements.

CHAPTER 18

Hydroxy Acids; Optical Isomerism

A number of hydroxy acids occur naturally as, for example, malic acid in many fruits, tartaric acid in grapes, and citric acid in lemons. In addition to their importance as naturally occurring substances they are of interest in connection with the phenomenon of optical isomerism.

Types of Hydroxy Acids. The main types are *alpha-*, *beta-*, *gamma-*, and *delta*-hydroxy acids (I to IV respectively).

The position of the hydroxyl group relative to the carboxyl group is important, for the different types may differ markedly in regard to reactions and methods of preparation.

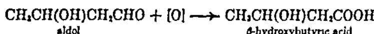
Preparation. Sometimes the *gamma-* and *delta*-hydroxy acids are obtained in the form of the lactones. Usually acidification of a concentrated aqueous solution of a soluble salt of the acid gives the free acid as a separate phase. However, some acids (glycolic, lactic) are very soluble in water and do not separate.

1. *Oxidation of di- or polyhydric alcohols* having at least one primary alcohol group.



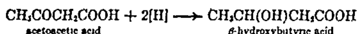
Dilute nitric acid often is satisfactory. The reaction above can be accomplished by air in the presence of platinum sponge. Usually, however, the product is a mixture containing some carbonyl compound because of oxidation of the other alcohol group.

2. *Oxidation of hydroxy aldehydes.* A number of β-hydroxy aldehydes are available from the aldol condensation (p. 272).



The reagent should be one that preferentially oxidizes aldehydes, for example silver oxide.

3. *Reduction of aldehydic or ketonic acids.* This is a generally useful method, since many β-oxo acids can be synthesized from acetoacetic ester, or by some modification of the Claisen condensation (p. 322).



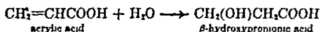
The reduction may be accomplished by means of reagents that reduce aldehydes and ketones (p. 262). The carbonyl group is much more easily reduced than the carboxyl group.

4. *Hydrolysis of halogenated acids.* This usually proceeds smoothly. However when the halogen atom is *beta*, unsaturation may be the main reaction (p. 207).

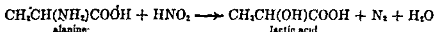


The acid may be heated with water or preferably with aqueous base, for example silver oxide, calcium hydroxide, or sodium hydroxide.

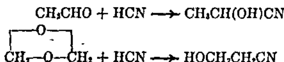
5. *Hydration of α-unsaturated acids.* This results in β-hydroxy acids (p. 199).



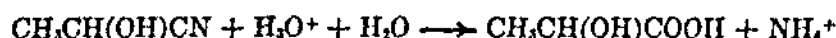
6. *Nitrosation of amino acids.* This is a characteristic reaction of the amino group (p. 357). Results are best with α-amino acids (Chap. 40).



7. *Hydrolysis of cyanohydrins.* α-Cyanohydrins are formed by the action of hydrocyanic acid on aldehydes and ketones (p. 269), β-cyanohydrins by addition of hydrogen cyanide to alkylene oxides (1,2-epoxyalkanes, p. 242) or by reaction of chlorohydrins (bromohydrins) with metallic cyanides.

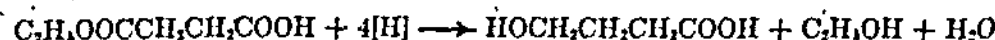


When heated with concentrated hydrochloric acid α-cyanohydrins are changed to α-hydroxyacids.



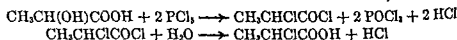
This is one of the most convenient methods for the preparation of α-hydroxy acids. A β-cyanohydrin usually is saponified with a base.

8. *Reduction of half esters of dibasic acids.* This method is especially useful for ω-hydroxy acids of four or more carbon atoms.



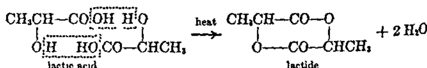
Reactions of Hydroxy Acids. Neutralization by bases and esterification by alcohols are characteristic reactions of the carboxyl group. Esterification of the alcoholic hydroxyl group by acid chlorides or anhydrides usually is possible Controlled oxidation usually leads to the formation of an aldehydic or dibasic acid if the hydroxyl group is primary, or of a ketonic acid if secondary. Complexes are formed between α-hydroxy acids and a variety of heavy metallic ions. The ones with ferric ion are colored yellow. This formation of the yellow color may serve as a test. Cupric complexes are a deep blue. The best known is the one with tartaric acid (see Fehling's Solution p. 311). Usually these complexes are stable under basic conditions.

Replacement of the alcoholic hydroxyl group by a halogen atom is best done with an inorganic acid halide. Lactic acid, for example, gives α-chloropropionyl chloride, and this is converted into α-chloropropionic acid by the action of water.

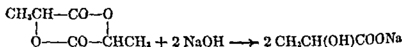


The most interesting reactions are those of self-esterification, as when an acid is heated alone or in the presence of an acidic catalyst, or often when attempt is made to isolate it by evaporation of a solution containing it. The three types of compounds which may result are unsaturated acids, lactides, and lactones.

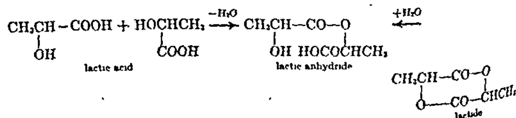
A characteristic reaction of α-hydroxy acids is the formation of a *lactide*, a cyclic ester involving two molecules of acid.



Lactides have rings of six atoms, *viz.*, four carbon and two oxygen atoms, similar to the ring of dioxane (p. 243). The ring is opened by a base, thus indicating the ester character of the lactide.

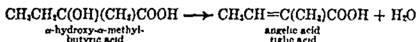


A so-called "anhydride" is an intermediate between the free acid and the lactide. It is the first product in the self-esterification of the α-hydroxy acid, or in the hydrolysis of the lactide.

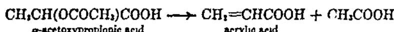


The two similar products derived from glycolic acid are called glycolic anhydride and glycolide respectively. In general, cyclic esters of α-hydroxy acids are called **lactides**.

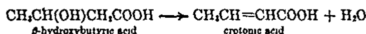
Besides lactide formation, α-hydroxy acids can also undergo decomposition to unsaturated acids. When the α-carbon is tertiary, this often can be accomplished merely by heating with a neutral type of dehydrating catalyst, for example aluminum oxide, and distilling over the more volatile unsaturated acid.



In industry acetates of α-hydroxy acids are pyrolyzed by passage in the vapor state over hot dehydration catalysts.

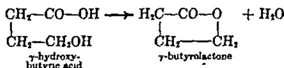


When β-hydroxy acids are heated under mildly acidic conditions as, for example, with sodium bisulfate, the corresponding α-unsaturated acid distils.

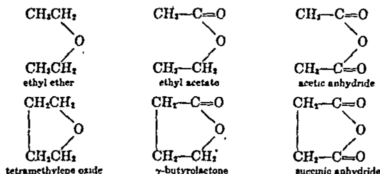


Usually the acid formed is the one that most readily hydrates, *viz.*, the *alpha*-unsaturated acid (p. 199). Thus it is evident that this reaction resembles other dehydration reactions in being reversible, since β-hydroxy acids often can be prepared by hydration.

When a γ-hydroxy acid is heated, intramolecular esterification takes place with the formation of a **lactone**, which is a cyclic ester.



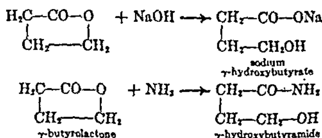
Like esters, which are intermediate between ethers and anhydrides, lactones are intermediate between cyclic ethers and cyclic anhydrides.



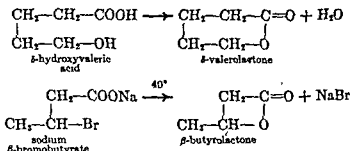
Sometimes the lactone is formed when attempt is made to isolate the acid. There is an equilibrium in solution between the free acid and the lactone, and,

this usually is slowly reached at ordinary temperature. In general the lactone is less soluble in water and more volatile than the hydroxy acid. Removal of the lactone by means of either property will upset the equilibrium. Many γ-hydroxy acids *are not known in the free state but only in combination as,* for example, in salts or esters.

Like other esters, lactones react with bases and with ammonia, with opening of the lactone ring. In the first case, salts are formed; in the second, amides. Alkali carbonates react only slowly.



Lactones are formed from δ-hydroxy acids, but less easily than from γ-acids. Lactones are known even from some β-hydroxy acids.



In ease of formation, γ-lactones as a group rank first, then δ-lactones, then β-lactones. This recalls *the ease of formation of cycloalkanes* (p. 99). The bond angle of an oxygen molecule is 111° (as in methyl ether, Table 6, p. 14), not greatly different from the tetrahedral angle of carbon. Thus the five-membered γ-lactone ring is analogous to the cyclopentane ring; the six-membered δ-lactone ring is analogous to the cyclohexane ring; and the four-membered β-lactone ring is analogous to the cyclobutane ring.

As with γ-lactones, there is an equilibrium in aqueous solution between other lactones and the corresponding acids. However, in these cases the equilibrium is not as favorable to the lactone. They react readily with bases, ammonia, etc., with opening of the lactone ring, and *β-lactones usually react* readily with water.

Linear polyesters result when a lactone ring would be seven-membered, or larger, owing to the fact that intermolecular reaction is faster than *intramolecular reaction.* The high polymer reaction usually accompanies lactide and lactone formation, also. The reaction is similar to the reaction of dibasic acids with glycols, except that the carboxyl group and the alcoholic hydroxyl group are in the same molecule.

Lactones can be obtained by depolymerization of these linear polyesters, usually by heating under controlled conditions at reduced pressure. The lactone distils as formed. In this way the lactone of ω-hydroxypentadecanoic acid, $HO(CH_2)_{14}COOH$, which is responsible for the musklike odor of angelica root, has been prepared experimentally. Lactones having large rings are less reactive than are ordinary lactones.

OPTICAL ISOMERISM

A large number of organic compounds possess optical activity, that is, they rotate the plane of plane-polarized light. This is light in which the vibrations are in one plane only, an effect produced by means of a polarizing lens, the polarizer. This is composed of plates of fluorspar so arranged as to exclude all light except that vibrating in one plane, and is called a Nichol prism. The degree of rotation of plane-polarized light is determined by passing the light through a tube containing the substance in liquid form, either as a pure liquid or in solution. The affected light is examined by passing through another Nichol prism, the analyzer. The specific rotation of a substance is the rotation resulting when light passes through 1 dm. of the liquid containing 1 g. per ml. In order to obtain the specific rotation, the observed rotation is divided by the density in the case of a pure liquid, or the concentration must be taken into account in the case of a solution. The relation between the observed rotation, $\alpha^{20}{}_D$, at a given temperature, say 20°, with a monochromatic light, say that of the sodium *D* line. and the specific rotation, $[\alpha]^{20}{}_D$, is given by the equation

$$[\alpha]^{20}{}_D = v\alpha^{20}{}_D/lw$$

where v is the volume of solution in milliliters containing w grams of solute, and l is the length of the tube in decimeters. For a pure liquid this becomes

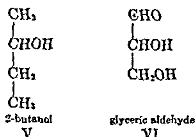
$$[\alpha]^{20}{}_D = \alpha^{20}{}_D/ld$$

where d is the density of the liquid. Rotations preferably are reported for 20 or 25°. Other monochromatic light is used also.

A substance that rotates the plane of polarized light to the right is called dextrorotatory, one to the left, levorotatory. For each dextrorotatory organic compound there is a theoretically possible levorotatory compound, rotating the same extent to the left that the other does to the right, and having the same physical properties as the other compound. The only difference between the two is shown by the effect on light. Two such pairs of compounds are called optical isomers. They are sometimes spoken of as **enantiamorphs**, a term familiar to crystallographers, or **optical opposites**, or **antipodes.**

An organic compound that rotates the plane of polarized light does not possess an element of symmetry. Generally the lack of symmetry is due to the presence of four different atoms or groups in combination with one carbon atom. Such a carbon atom is called an **asymmetric carbon atom.** This concept of the asymmetric carbon atom was advanced independently in 1874

by van't Hoff and Le Bel as an explanation of optical activity. Two of the simplest compounds having asymmetric carbon atoms are 2-butanol, V, and glyceric aldehyde, VI.



In each case carbon atom C-2 (numbering from the top) is asymmetric, for it is attached to four different atoms or groups: in V to CH_3, H, OH, and C_2H_5; in VI to CHO, H, OH, and CH_2OH.

The arrangement of four groups in space about an asymmetric carbon atom is best shown by means of tetrahedral models. However, it can also be shown by means of projection formulas, which are more convenient for a textbook than attempting to show tetrahedra on a plane surface. One method of projecting the tetrahedral arrangement onto a plane surface is shown in Figure 14. Here the tetrahedron, VII, is drawn with a carbon atom at the center



Figure 14 • Relation of Projection Formula to Tetrahedral Arrangement about a Carbon Atom

with two faces towards, and one vertical edge away from the observer. In VIII, lines are drawn to the four corners, those directed in front of the plane of the paper being heavier than those directed behind this plane. *In IX these lines, which are the four bonds of the carbon atoms, are drawn without the tetrahedron. In X these are flattened out into a true projection formula.* The limitation imposed by the use of projection formulas does not permit their removal from the plane as written. They can be rotated through any desired angle, but no groups can be interchanged. The clockwise order of groups about the asymmetric carbon atom must remain the same.

In VIII and IX the other carbon atoms of the carbon chains of V and VI lie in a plane behind that of the asymmetric carbon atom, while the H and OH groups lie in front. It is necessary that the projecting always be done in the same way. The other method would involve projecting the tetrahedron, VII, after it has been rotated on its vertical axis through an angle of 180°.

When projections are made of two possible tetrahedral arrangements of the groups attached to the asymmetric carbon atoms of 2-butanol, V, and of glyceric aldehyde, VI, two possibilities are found for each, *viz.*, XI and XII, XIII and XIV, Figure 15.

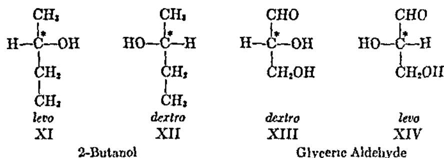


Figure 15 · Stereoisomeric Forms of 2-Butanol and Glyceric Aldehyde. Asterisks indicate asymmetric carbon atoms.

It is evident that XI and XII are not superposable, neither are XIII and XIV, because of the limitations mentioned above. However, XI and XII are related to each other as an object and its mirror image, or as a person's right and left hand. A similar relationship holds for XIII and XIV. These formulas explain the existence of optical isomers, for example, *dextro-* and *levo-*2-butanol, and *dextro-* and *levo-*glyceric aldehyde; likewise the identity in other physical properties of the *dextro-* with the *levo-*form. Polarized light is affected by the dissimilar arrangement, but other physical properties, as for example, melting point, boiling point, specific gravity, and refractive index are not, since two optical opposites have identical structures. The only difference is arrangement in space. This example of **stereoisomerism** is called **optical isomerism,** to differentiate it from geometrical, or *cis,trans*-isomerism (p. 64).

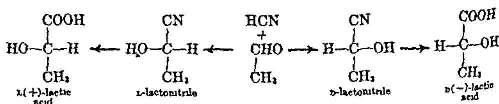
Glyceric aldehyde is important in stereo chemistry, for it is the basic compound to which is referred the **configuration,** *i.e.*, the space arrangement about the asymmetric carbon atom, of a large number of optically active organic compounds. It is selected because of its relationship to the sugars (Chap. 42). When the hydrogen and hydroxyl groups are projected forward, as already described (Fig. 14), the hydroxyl group of glyceric aldehyde is written on the right, as shown by formula XIII, for the dextrorotatory isomer, and to the left, formula XIV, for the levorotatory isomer, as proposed originally by Emil Fischer in 1891. This arbitrarily assigned configuration has been shown, by calculations of a theoretical nature, to be the correct absolute configuration.

The active forms of the aldehyde often are designated as *d*-glyceric aldehyde and *l*-glyceric aldehyde, respectively. Historically this has been the usual method of indicating the sign of rotation of most optically active compounds, but within recent years much confusion has arisen, because many chemists have used the *d-* and *l*-prefixes to indicate configurational relationships. When this is done (+) and (−) are used to indicate the *dextro-* and *levo*-isomers, respectively. Recently a new method has been recommended

by a committee of the American Chemical Society, so as to avoid this confusion. According to this, (+) and (−) indicate the sign of rotation, while D and L indicate configurational relationships. This method is adopted for this text. Thus XIII is D(+)-glyceric aldehyde and XIV is L(−)-glyceric aldehyde.

An inactive compound is obtained by mixing equal amounts of the *dextro*- and *levo*-isomers. This is designated as the *dl* or DL or, sometimes, racemic substance. It is sometimes called the externally compensated form, for the rotation produced by the *dextro*-isomer is compensated by that of the *levo*-isomer. By suitable methods the DL-compound can be **resolved,** *i.e.*, separated into the active forms as described later under Resolution. Some physical properties of the inactive form are similar to those of the active form: for example, in the case of liquids, the boiling point, density, and refractive index are alike However, in the case of solids, the density, refractive index, melting point, and solubility may be different. Sometimes the inactive product has a higher melting point than the active forms. This indicates that compound formation has taken place. In such a case the inactive form is called **a racemic compound** or **racemate** (p. 312).

A synthetic product resulting from the reaction of two inactive compounds is likewise inactive even when an asymmetric carbon atom is formed. Thus, in the reaction of acetaldehyde with hydrogen cyanide to form lactonitrile, equal amounts of the two possible stereoisomers are formed. When the inactive nitrile is converted into lactic acid, this also is inactive, since equal amounts of the (+)- and (−)-acid are present



The number of stereoisomeric forms is doubled for each additional asymmetric carbon atom. Thus there are four stereoisomers of α,β-dihydroxybutyric acid, $CH_3\overset{*}{C}HOH\overset{*}{C}HOHCOOH$, and eight of α,β,γ-trihydroxyvaleric acid This relationship holds so long as the molecule is unsymmetrical The number of stereoisomers is then equal to 2^n, where n is the number of asymmetric carbon atoms.

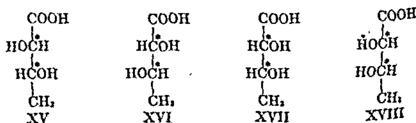


Figure 16 • Stereoisomeric α,β-Dihydroxybutyric Acids.

constitute one pair of enantiamorphs (antipodes, optical opposites) while XVII and XVIII constitute another such pair. There are two DL (or *dl*)-acids, one composed of equal amounts of XV and XVI, the other of equal amounts of XVII and XVIII. Stereoisomers which are not antipodes, as for example XV and XVII, sometimes are referred to as **diastereomers** (or diastereoisomers).

The importance of always writing the carbon chain vertically is shown by the formulas of Figure 17.

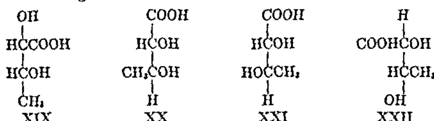


Figure 17 · Other Formulas, Not Recommended, of the α,β-Dihydroxybutyric Acids.

These do not represent additional compounds, however, because each one is identical with one of the first four as follows: XIX with XV, XX with XVI, XXI with XVII, XXII with XVIII. It will be observed that in each case the order in which the groups are arranged about each of the two asymmetric carbon atoms is the same for any pair of formulas. In XV and XIX, for example, the order of the groups about the upper carbon atom in a clockwise direction is COOH, H, OH. XV and XIX simply represent different projections of the same spatial arrangement about this carbon atom. Needless confusion in the use of projection formulas is avoided by writing the carbon chain in the vertical position and the substituents in the horizontal.

Configurational Relationships. Lactic, malic, tartaric, and glyceric acids have been related to glyceric aldehyde by means of changes that do not affect the asymmetric carbon atom (Fig. 18). It is seen that the isomers which are related to dextrorotatory glyceraldehyde are (−)-glyceric acid, (−)-lactic acid, and (+)-malic acid. There appears to be a contradiction in the case of tartaric acid, for both the (−) and (+) acid can be related directly to D(+)-glyceraldehyde. This is because there are two asymmetric carbon atoms in tartaric acid. When the relationship is made by means of the cyanohydrin reaction, carbon atom C-3 has the same configuration as the carbon atom of glyceric aldehyde, and when it is made by means of the Hofman degradation (Chap. 22), carbon atom C-2 has this same configuration. The contradiction is resolved by always referring the configuration to the lowest (highest numbered) asymmetric carbon atom in the chain, which in the case of tartaric acid is the third carbon atom. On this basis levorotatory tartaric acid belongs to the same family as D(+)-glyceric aldehyde, *i.e.*, the D-family. This introduces an unfortunate contradiction; because in the past (+)-tartaric acid has been called *d*-tartaric acid, and this name is in common use.

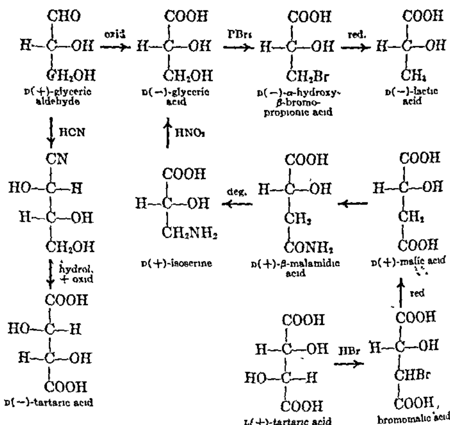


Figure 18 · Configurational Relationship of Hydroxy Acids.

INDIVIDUAL HYDROXY ACIDS

Occurrence of Hydroxy Acids. Sometimes the acids are present uncombined, but more often they are in the form of a salt — potassium, magnesium, or calcium. A general method of isolation, discovered by Scheele about 1770, consists in adding milk of lime to an aqueous solution containing the acid, collecting the precipitated calcium salt and decomposing it with dilute sulfuric acid. Evaporation of the resulting solution yields the free acid. The calcium salt may be precipitated also by adding a soluble calcium salt to a neutral solution of a soluble salt of the hydroxy acid.

Glycolic acid is found in unripe grapes and at times in other plants, for example, beets. Lactic acid occurs as the dextrorotatory form in muscle and blood (called sarcolactic acid in this connection). The concentration of lactic acid in muscle increases with muscular activity. The *dextro*-acid is formed in the fermentation of sucrose or glucose by *Streptococcus lactis*. Industrially, lactic acid (dextro or inactive) is produced from sucrose, glucose, or maltose by fermentation with a variety of bacteria, for example, *Lactobacillus delbruckii*, *Lactobacillus bulgaricus*, *Bacillus dextrolacticus*, or *Streptococcus lactis*. Of these the first two are preferred. With the third, large yields of the *dextro*-acid can be obtained from levulose. The *levo*-acid is formed with other bacteria, for example, *Lactobacillus caucasicus*. Lactose (milk sugar) is not fermented by *L. delbruckii*. Lactic acid is present in sour milk and in other food products in which the lactic acid fermentation has taken place, for example, sauerkraut, pickled cucumbers, cheese, and ensilage. It is present in gastric juice. It was from sour milk that lactic acid was first isolated by Scheele in 1780.

Malic acid is found as the levorotatory form in many fruits, particularly in berries

of the mountain ash and berries of *Berberis vulgaris* (barberries). It is present in gooseberries, cherries, and strawberries, and also in unripe apples (*L., malum*). It was from this last source that Scheele first isolated malic acid in 1785. It is one of the most widely distributed substances in the vegetable kingdom and is found in fruits, seeds, roots, and leaves of a great many plants.

Tartaric acid as the *dextro*-form is widely distributed in plants. The best source is the grape, where it is present as the acid potassium salt. This crystallizes when grape juice undergoes alcoholic fermentation to wine. In the crude form it is called argol, and after purification, **cream of tartar.** Argol has been known since ancient times, but Scheele in 1769 was the first to isolate tartaric acid. Inactive (racemic) tartaric acid is present, along with ordinary tartaric acid, in grapes from certain districts. It was discovered by Kistner in 1822.

Citric acid occurs in many fruits and berries, especially citrus fruits. The juice of lemons may run as high as 6 per cent of citric acid. It was discovered in 1784 by Scheele.

Physical Properties of Hydroxy Acids. It is evident from Table 60, which lists the more common hydroxy acids, that the boiling points and melting points are much higher than those of the unsubstituted acids. Their vapor pressures are so low that they cannot, in general, be distilled at atmospheric pressure without decomposition. They are stronger acids than the unsubstituted acids. They have high solubilities in water, and those of low melting point are miscible in all proportions with water. Their solubility in alcohol is usually less than in water, while in ether it is usually quite low.

It is interesting to note that whereas the melting point of (+−)-lactic acid is lower than the melting point of the active forms, the reverse is true of (+−)-malic and of (+−)-tartaric acids. The significance of this is pointed out under Racemates (p. 312).

TABLE 60 | Constants of Some Hydroxy Acids

ACID	M.P. °C	SP. GR. 20°/4°	SOLUBILITY IN		$K_a \times 10^5$		H_2O OF CRYST.
			H_2O at 25° g./100 g.	EtOH g./100 g.	K_1	K_2	
Citric	135[a]	1.5	240	43[b]	88	17	1
Glycolic	α63, β80		v. sol.		15		0
(+)-Lactic	52 8		v. sol.				0
(+−)-Lactic	16 8		misc.	91[c]	15		0
(−)-Malic	101	1.595	v. sol.		39	0 72	0
(+−)-Malic	130	1 601	138	27.6	40	0 55	0
(+)-Tartaric	170	1.760	147		90	0 39	0
(−)-Tartaric	170	1.760	147				
(+−)-Tartaric	205[a]	1.687	21.4	5 0	117	0 59	1
meso-Tartaric	140[a]	1 666	167		77	0 16	1

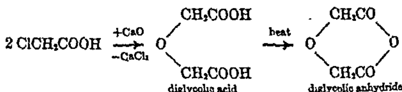
[a] Anhydrous. [b] At 15° [c] At 10°.

Glycolic Acid, Hydroxyacetic Acid, $HOCH_2COOH$. This is the simplest hydroxy acid. It is best prepared by heating a solution of sodium or potassium chloroacetate.



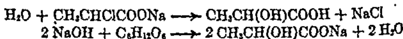
$$HOH + ClCH_2COOK \longrightarrow HOCH_2COOH + KCl$$

Besides glycolide and glycolic anhydride (p. 296) other compounds can be formed from two molecules of acid.



Lactic Acid, α-Hydroxypropionic Acid, $CH_3CH(OH)COOH$. Industrially this is produced by fermentation of sugar by means of microorganisms (p. 304). A culture of the bacillus, a nutrient medium (as, for example, milk), and calcium (or zinc) carbonate are added to an aqueous solution of sugar. The carbonate is added to neutralize the acid, since a low *p*H is detrimental to the fermentation process. Calcium (or zinc) lactate crystallizes out. This sometimes dissolves slowly because of the formation of butyric acid, the result of a second fermentation, the butyric acid fermentation. This converts lactic acid as well as sugar into butyric acid. Usually precautions are taken to prevent contamination by the butyric acid bacteria. The slightly soluble metallic lactate is decomposed by sulfuric acid.

Inactive lactic acid is produced by hydrolysis of α-chloropropionic acid, and by the action of caustic alkalies on glucose.

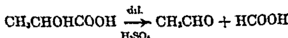


$$H_2O + CH_3CHClCOONa \longrightarrow CH_3CH(OH)COOH + NaCl$$
$$2\,NaOH + C_6H_{12}O_6 \longrightarrow 2\,CH_3CH(OH)COONa + 2\,H_2O$$

This last is a convenient method of preparation. Addition of a soluble calcium or zinc salt causes precipitation of the corresponding lactate. Lactic acid can be synthesized by the cyanohydrin reaction (p. 269).

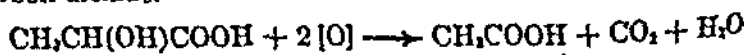
The *levo*-acid is related configurationally to D(+)-glyceric aldehyde (p. 304) and is designated as D(−)-lactic acid. The *dextro*-acid is L(+)-lactic acid. All the salts and esters of D(−)-lactic acid are dextrorotatory. By the action of ordinary green mold, *Penicillium glaucum*, on DL-lactic acid, L(+)- lactic acid is obtained, for D(−)-lactic acid is destroyed by the organism.

Lactide, m.p. 125°, b.p. 255°, is obtained by heating lactic acid under diminished pressure (p. 297). If the heating is done at atmospheric pressure, besides lactide formation another decomposition yields aldehyde, carbon monoxide, and water. This last is similar to the decomposition of lactic acid into aldehyde and formic acid when heated with dilute sulfuric acid.



$$CH_3CHOHCOOH \xrightarrow[H_2SO_4]{dil.} CH_3CHO + HCOOH$$

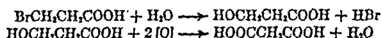
This is equivalent to a reversal of the cyanohydrin reaction, since hydrogen cyanide is the nitrile of formic acid. Oxidation of lactic acid by chromic acid yields acetic acid and carbon dioxide.



$$CH_3CH(OH)COOH + 2\,[O] \longrightarrow CH_3COOH + CO_2 + H_2O$$

Lactic acid is added to beverages such as lemonade. In tanning it is useful in removing lime from hides, and in the dyeing industry it sometimes serves as a reducing agent in chromation, *i.e.*, reduction of chromate (Chap. 46). In this industry antimony lactate serves as a mordant.

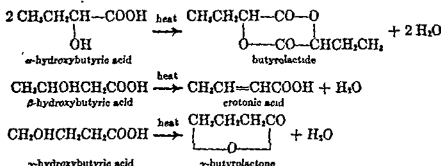
Hydracrylic Acid, β-Hydroxypropionic Acid, $HOCH_2CH_2COOH$. This is isomeric with lactic acid. Its preparation by the hydrolysis of β-bromopropionic acid and the formation of malonic acid on oxidation prove its structure.



$$BrCH_2CH_2COOH + H_2O \longrightarrow HOCH_2CH_2COOH + HBr$$
$$HOCH_2CH_2COOH + 2\,[O] \longrightarrow HOOCCH_2COOH + H_2O$$

Glyceric Acid, α,β-Dihydroxypropionic Acid, $HOCH_2CHOHCOOH$. The inactive acid is obtained from glycerol by oxidation with nitric acid. It has been resolved. The salts of the levorotatory acid, D(−)-glyceric acid (p. 304) are dextrorotatory.

Hydroxybutyric Acids. The main interest in the three structurally isomeric hydroxybutyric acids lies in their different behavior when heated. The α-acid is converted into butyrolactide, the β-acid mainly into crotonic acid, and the γ-acid into butyrolactone.

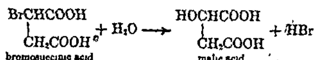


$$2\,CH_3CH_2CH(OH)COOH \xrightarrow{heat} \text{butyrolactide} + 2\,H_2O$$
$$CH_3CHOHCH_2COOH \xrightarrow{heat} CH_3CH{=}CHCOOH + H_2O$$
$$CH_2OHCH_2CH_2COOH \xrightarrow{heat} \gamma\text{-butyrolactone} + H_2O$$

Tartronic acid, hydroxymalonic acid, $HOCH(COOH)_2$, is the simplest monohydroxydibasic acid. It may be obtained by the hydrolysis of bromomalonic acid, a reaction which establishes its structure.

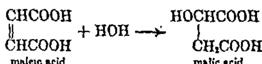
***Malic Acid,* Hydroxysuccinic Acid, $HOCH(COOH)CH_2COOH$.** Its occurrence and the relationship of the active forms to glyceraldehyde are both described on p. 304. The *dextro*-acid is D(+)-malic acid, and the *levo*-acid, L(−)-malic acid. Although the naturally occurring malic acid is levorotatory in dilute aqueous solution, it is dextrorotatory in concentrated solution. Its salts have a higher negative rotation in dilute solution than has the acid. The esters are levorotatory. With dilution the rotation of the acid decreases until it reaches a zero value and then on further dilution becomes negative.

The inactive form may be prepared by the hydrolysis of bromosuccinic acid, a reaction which proves its structure.

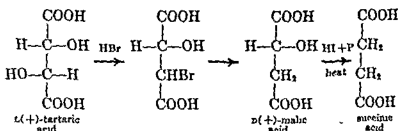


$$BrCH(COOH)CH_2COOH + H_2O \longrightarrow HOCH(COOH)CH_2COOH + HBr$$

The reaction is reversible ... formed in a reaction be- ... e bromosuccinic acid may ... fumaric acid and hydrobromic acid, either of these two organic acids could serve as a source of synthetic malic acid. A more convenient source is maleic acid, which undergoes hydration when heated with dilute aqueous sodium hydroxide at 100°. This is done industrially.



D(+)-Malic acid can be obtained from ordinary *dextro*-tartaric acid by reduction either directly by heating with hydriodic acid, which also may reduce malic to succinic acid, or by conversion first to bromomalic acid, then reduction.



Malic acid decomposes when heated. At 140 to 150° the principal product is fumaric acid, but when the temperature is higher maleic anhydride distils (p. 203). Malic acid has a pleasant acid flavor and is used in soft drinks and in different food products.

Tartaric Acid, Dihydroxysuccinic Acid, HOOCCHOHCHOHCOOH. Four dihydroxysuccinic acids are known, *viz.*, *dextro*-tartaric, *levo*-tartaric, *meso*-tartaric, and racemic tartaric acids (see Table 60).

The possible stereoisomeric forms corresponding to those of α,β-dihydroxybutyric acid, XV, XVI, XVII, and XVIII, page 302, are XXIII, XXIV, XXV, and XXVI, respectively, Figure 19.

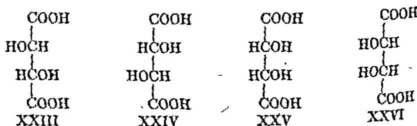


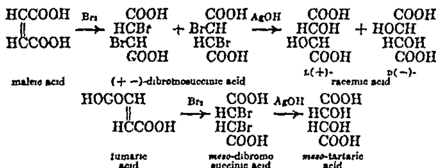
Figure 19 · Four Ways of Writing Stereoisomeric Dihydroxysuccinic Acids.

It is evident that XXIII and XXIV are mirror images and cannot be superposed, and that XXV and XXVI, although written as mirror images can be superposed, merely by rotating one through an angle of 180°. Thus these two are identical. Therefore there are actually only three theoretically possible stereoisomeric tartaric acids, and actually only three are known, *viz.*, *dextro*, *levo*, and the inactive *meso* acid. The fourth, a second inactive form, is a mixture of equal amounts of the *dextro*- and *levo*- forms as discovered by Pasteur (see Resolution). It is called racemic tartaric acid or sometimes racemic acid. The reason for the inactivity of the *meso*-isomer is given later under Internal Compensation (p. 311).

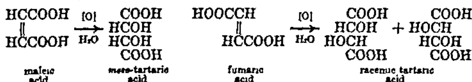
Ordinary *dextro*-tartaric acid, commonly indicated as *d*-tartaric acid, is XXI[illegible] (p. 304). According to the nomenclature preferred here it is L(+)-tartaric acid (p. 304), or the sign of rotation only is given, it is (+)-tartaric acid Likewise, XXIII, formerly "*l*-tartaric acid," is preferably D(−)-tartaric acid, or (−)-tartaric acid The inactive form, *meso*-tartaric acid is XXV, sometimes designated as *i*-tartaric acid. Racemic

acid is an equimolal mixture of XXIII and XXIV, and is *dl*-, DL-, or (+ −)-tartaric acid, sometimes *rac*- (for racemic). The occurrence of tartaric acid is described on page 304.

The preparation of the inactive tartaric acids is accomplished by a method that establishes their structures. Dibromosuccinic acids, prepared by the action of bromine on maleic and fumaric acids, on hydrolysis yield respectively racemic and *meso*-tartaric acids. This establishes these acids as dihydroxysuccinic acids.

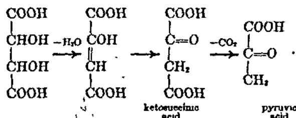


The way bromine adds to the double bond of these organic acids is typical. The bromine atoms do not become attached to the same sides of the two carbon atoms but to opposite sides. The reaction therefore is spoken of as a *trans*-addition, which is the normal reaction, in contradiction to *cis*-addition, which is much less common. However, permanganate oxidation usually proceeds via *cis*-addition, as the formation of the inactive tartaric acids shows.

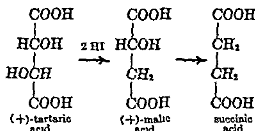


Thus maleic acid gives racemic acid through bromine addition, and the *meso*-acid by permanganate oxidation. A total synthesis of tartaric acid (synthesis from the elements) can be accomplished through the steps: acetylene, ethylene, ethylene bromide, ethylene cyanide, succinic acid, bromosuccinic acid, maleic (fumaric) acid, tartaric acid.

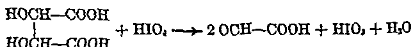
When heated above its melting point, tartaric acid loses water and is converted into different anhydrides, the nature of which depends upon the duration and intensity of heating. At higher temperatures it turns brown and possesses an odor of caramel. On still stronger heating it chars and pyruvic acid (pyroracemic acid) distils. This is believed to result by loss of water. At first an intermediate enol is formed; this undergoes a normal reaction of isomerization to ketosuccinic acid and this undergoes normal decarboxylation to pyruvic acid.



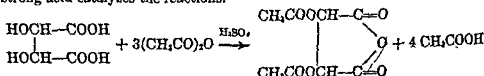
Tartaric acid when heated with hydriodic acid is reduced, first to malic acid, then to succinic acid. The ordinary *dextro*-acid yields *dextro*-malic acid, not the naturally occurring *levo*-isomer.



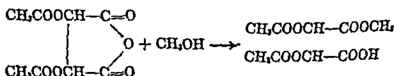
Strong oxidizing agents convert tartaric acid to oxalic acid. Ammoniacal silver gives a silver mirror. Hydrogen peroxide in the presence of silver salts gives dihydroxymaleic acid. Periodic acid oxidizes tartaric acid to glyoxalic acid.



Tartaric acid forms esters at the carboxyl groups, ethers or esters at the alcoholic hydroxyl groups. An interesting reaction is the one with acetic anhydride, which esterifies the hydroxyl groups and also causes anhydride formation. A small amount of strong acid catalyzes the reactions.

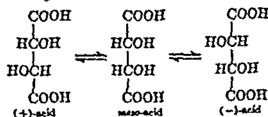


The product, diacetyltartaric anhydride (diacetoxysuccinic anhydride) reacts readily with alcohols.



With methyl alcohol the product is monomethyl diacetyltartrate. This reaction has been used for resolving alcohols having an asymmetric carbon atom (see Resolution, p. 313).

When heated in aqueous sodium hydroxide, (+)-tartaric acid is slowly converted first to *meso*-tartaric acid, finally to a mixture of *meso* and racemic acids. This involves a stereochemical change that is essentially a racemization process (p. 314).



Separation of the *meso*-acid from the racemic is accomplished by means of the acid potassium salt, the *meso*-salt being readily soluble in water, those of active and racemic acids being slightly soluble.

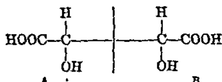
Ordinary tartaric acid in dilute aqueous solution is dextrorotatory, but the supersaturated solution is levorotatory. The esters and salts are dextrorotatory. The slightly soluble potassium salts of the active and racemic acids are dissolved by the addition either of potassium hydroxide or of a strong acid, because of the formation, respectively, of soluble potassium tartrate or tartaric acid.

Tartaric acid is used in the dye industry as a mordant and as a component of the dye bath. The acid is added to some food products, in particular lemonade powders. The acid potassium salt is used in large quantities in the manufacture of baking powders. These contain cream of tartar, sodium bicarbonate, and starch. Rochelle salt, sodium potassium tartrate, is used in the preparation of Fehling's solution and in medicine as a purgative and diuretic. Tartar emetic, potassium antimonyl tartrate, KOOC—CHOH—CHOH—COO(SbO)·$\frac{1}{2}$ H_2O, is a useful mordant in dyeing and is used in medicine as an emetic.

Fehling's Solution. This is made by mixing equal volumes of two solutions just before use, *viz.*, I, 34.639 g. of pure copper sulfate pentahydrate in 500.0 ml. of aqueous solution and II, 173 g. of Rochelle salt and 50 g. of sodium hydroxide in 500 0 ml. of aqueous solution. Cupric ion forms a soluble one-to-one complex with tartrate ion which is deep blue. In this the copper is believed to be coordinated with the alcoholic oxygen atoms. When this solution, in a vertical tube, is covered with a colorless solution of sodium sulfate, the copper migrates upward when the anode is in the upper liquid and the cathode in the lower.

Fehling's solution is reduced to insoluble red cuprous oxide when an aldehyde is added to the hot solution. The reagent is especially useful in sugar chemistry to differentiate reducing sugars such as glucose and fructose from nonreducing sugars such as sucrose. The extent of the reduction can be measured by determining the [illegible]

Internal Compensation. *meso*-Tartaric acid is optically inactive as a result of internal compensation. Racemic acid is inactive as a result of external compensation, *i.e.*, the rotation produced by a molecule of *dextro*-acid is compensated by a molecule of the *levo*-acid. The compensation in the case of the *meso*-acid is entirely within the molecule, one half of which is the mirror image of the other half:



In the formula above the two halves, A and B, are mirror images of each other and have exactly opposite effects upon the plane of polarized light. [illegible]

molecule has a plane of symmetry. In all such cases it will be found that the original molecule and its mirror image are identical. Such compounds are

usually called *meso*-forms and belong to the *indivisible* type because, unlike the externally compensated forms, they cannot be divided into *dextro*- and *levo*-antipodes. They often are designated by means of the prefix *i*, for example, *i*-tartaric acid.

Racemates. Racemic acid melts at 206°, a higher temperature than either of the active forms (170°), whereas inactive lactic acid melts at 16.8°, a lower temperature than the active form (52.8°) (*Table 60, p. 305*). If the melting points of mixtures of the *dextro*- and *levo*-forms of a substance are plotted as ordinates against the composition as abscissae, the system will conform to one of the three types of curves shown in Figure 20, provided the solid phases do not form mixed crystals (solid solution) with the inactive form or with each other.



Figure 20 · Melting-Point Curves

XXVII represents a system in which there is no racemate. In such a system, the solid phase that separates along one of the asymptotes is the pure *dextro*-isomer, and along the other is the pure *levo*. In XXVIII and XXIX it is evident that the middle section of the curve is due to the existence of a third compound, composed of equal amounts of the two active forms. At any portion of these curves a pure solid is in equilibrium with the liquid. The solid is the pure (+)- or (−)-isomer along the outside portions of the curve, and the pure addition compound or racemate along the middle portion. When the (+−)-mixture has a melting point above that of the active forms, one will know at once that he is dealing with a type of addition compound, and that the system belongs to type XXIX above. If, however, the melting point is below that of the active forms, the system may belong either to type XXVII or to type XXVIII. A decision can be made by taking the melting points of a number of mixtures of the (+)- and (−)-forms. When the system conforms to XXVIII or XXIX, the active isomers combine to form a racemate, or racemic compound, which is a loose combination of equal amounts of the two active forms.

The method of melting points is not generally applicable to salts, many of which decompose before they melt. In such a case the existence of a racemate can be established by adding some of the pure solid *dextro*- or *levo*-isomer to a saturated solution of the (+−)-compound. If the latter is not a racemate, no change is observed in the rotation of the solution since the solvent is already saturated with respect to both of the active isomers. But if the solution acquires a rotation, it means that the solid added has dissolved and

the solution was saturated with respect to a racemate, but not to the active isomer.

The forces that are responsible for racemate formation must be quite weak since in solution the molecular weights are those corresponding to one of the active forms. Moreover, volatile racemates have normal vapor densities.

Resolution of Inactive Compounds. The investigation of Pasteur on the resolution of racemic tartaric acid is one of the classics of chemistry. Up to 1848 two tartaric acids were known, ordinary *(dextro)* tartaric acid and racemic acid. It was known that the former was dextrorotatory and the latter inactive, but the relation of one to the other was not understood. Pasteur noted through the microscope that when a solution of sodium ammonium racemate was allowed to evaporate spontaneously, the tiny crystals that separated out were of two types, depending upon the position of certain small facets on the crystals. These two types were not identical but were related to each other as an object and its mirror image. He then painstakingly separated the small crystals into two groups and found that when they were separately dissolved in water, one group turned the plane of polarized light to the right, the other to the left. He had thus effected a resolution of a salt of racemic acid into its two antipodes. Next he showed that one of these is identical with the salt of *dextro*-tartaric acid. It was not until 1874 that van't Hoff and Le Bel independently advanced the theory of the asymmetric carbon atoms as an explanation of optical activity.

There are three methods, all developed by Pasteur, for obtaining active isomers from DL-compounds, as follows: (1) spontaneous crystallization; (2) the biochemical method; (3) combination with a second, optically active compound. Separation by spontaneous crystallization is relatively rare. Even in the case of sodium ammonium tartrate it takes place only below 28°. Above that temperature the racemic salt separates.

In the second (the biochemical) method one form is destroyed by some microorganism. On the addition of ordinary green mold, *Penicillium glaucum*, to a dilute solution of tartaric acid the solution becomes levorotatory through the destruction of the *dextro* form. The enzyme responsible for the disappearance of one form is itself optically active and thus is specific in its action. This selective effect is an example of **specificity.**

In the third method, the usual chemical method, advantage is taken of the reactivity of some functional group of the DL-compound so as to cause it to react with another optically active compound to produce two diastereomeric solid compounds. These two differ in physical properties. The difference in solubility allows the two to be separated from each other by crystallization. The final step is the decomposition of a pure diastereomer so as to regenerate the original compound as one of the two optical isomers. If both diastereomers can be obtained pure, then both optical isomers can be obtained pure.

The easiest types of compounds to resolve are acids and bases. This is because it is possible to convert these readily to solid salts, merely by addition

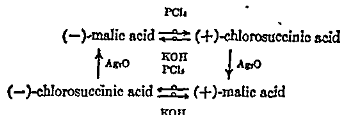
of bases and acids, respectively, and also because many naturally occurring bases (alkaloids) and acids are optically active and are readily available. For example, when (+−)-malic acid and the alkaloid, cinchonine, are heated in methanol solution, two diastereomers are formed, namely, (+)-cinchonine (−)-malate and (+)-cinchonine (+)-malate. These are not enantiamorphs, for the mirror image of (+)-cinchonine (−)-malate is (−)-cinchonine (+)-malate. On cooling, (+)-cinchonine (−)-malate separates almost completely (solubility is 2 per cent), and (+)-cinchonine (+)-malate largely remains in solution. Likewise (+)-cinchonine (−)-tartrate is less soluble in water than (+) cinchonine (+)-tartrate. Other active bases commonly employed for resolving acids are brucine, cinchonidine, menthylamine, morphine, quinine, and strychnine. Optically active acids useful in resolving inactive bases are camphoric acid, camphor-10-sulfonic acid, malic acid, quinic acid, tartaric acid, and diacetyltartaric acid.

Alcohols are not so easily resolved. One method, of limited application, is the formation of an ester with an optically active acid of high enough melting point to give a solid ester. Another, more generally useful, method depends upon forming the half ester of a dibasic acid, as with succinic anhydride or phthalic anhydride, and resolving these half esters by means of an active base, as described in the preceding paragraph. The active alcohol is recovered by saponification of the half ester.

Racemization. When an optically active substance is converted into the inactive form, the process is called racemization. Compounds vary in the ease with which this is accomplished; the active lactic acids and many other active hydroxy acids are stable at ordinary temperature, even over long periods of time, and must be strongly heated to bring about the change. Racemization of α-hydroxy acids is promoted by the presence of alkali.

The dextrorotatory isobutyl bromopropionate and other compounds containing a bromine atom attached to the asymmetric atom gradually become optically inactive at ordinary temperature after being kept for three or four years. The velocity of transformation, which in the case of the hydroxy acids at ordinary temperature is too small to be measured, has in the case of the *alpha*-bromo acids a measurable value. Some optically active compounds racemize so rapidly that it is difficult to obtain them pure. Racemization is effected when one half of the optically active compound is converted into its antipode.

Optical or "Walden" Inversion. Walden found (1895) that levorotatory chlorosuccinic acid is converted into levorotatory malic acid by the action of silver oxide or of water alone and into dextrorotatory malic acid when a strong base is used. Likewise dextrorotatory chlorosuccinic acid yields dextrorotatory malic acid with silver oxide, levorotatory malic acid with potassium hydroxide. Silver oxide gives an acid of the same sign, potassium hydroxide one of opposite sign. Reversing the reaction, he found that (−)-malic acid is converted into (+)-chlorosuccinic acid and (+)-malic acid into (−)-chlorosuccinic acid by the action of phosphorus pentachloride. The transformations possible are shown on the next page.



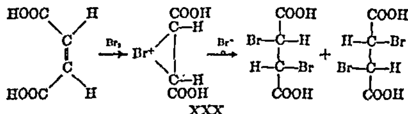
It is thus possible to prepare (+)-malic acid from (−)-malic acid by reacting first with phosphorus pentachloride and then with silver oxide. In this way the direction of rotation is "inverted," and on this account the operation is called an inversion. It is evident that the inversion does not take place at both steps in the process, otherwise there would be no change in the sign of rotation of the resulting acid. Consequently at one step in the process an inversion takes place, and at the other step there is no inversion.

Inversion of configuration during a replacement (more strictly displacement) reaction is now known to be the normal type of reaction because it is a result of the so-called "umbrella effect" (p. 113). The entering negative ion approaches the asymmetric carbon atom on the side opposite to the group being displaced, owing to the influence of the dipole moment of the bond joining this group to the carbon atom. Thus the new bond is made on the opposite side of the carbon atom, and this causes inversion of configuration.

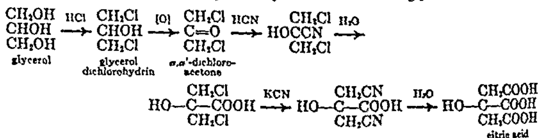
In the scheme above, inversion of configuration accompanies reactions with phosphorus pentachloride and potassium hydroxide, but not with silver oxide. Inversions are indicated by a looped arrow —ᐱ→. Silver oxide reacts by a different mechanism. This may involve two steps, each accompanied by an inversion. One step could be associated with adsorption on the solid silver oxide or silver halide, the other step the displacement reaction. Also, it is possible that the carboxyl group is responsible for a different mechanism. It is known now that some neighboring groups can be involved in displacement reactions through the formation of unstable intermediates, which then react with the reagent. Thus there could be two steps in the overall change, one when the intermediate is formed, the other when it reacts. The result of two inversions would be retention of configuration.

It is not possible to decide, on the basis of rotation, that an inversion has or has not taken place. It will be noted from page 304 that compounds having the same configuration, for example, glyceric aldehyde and glyceric acid, may have opposite signs of rotation.

The *trans*-addition of bromine to an olefinic double bond is explained as a two-step process: (1) the attachment of a positive bromine atom, without inversion, to form a reactive, cyclic intermediate, XXX, and (2) opening of the ring by a bromide ion reacting at either carbon with inversion of configuration. For the addition process there is thus one and only one inversion.



Citric Acid, $HO-C(CH_2OH)_2COOH$. Occurrence is mentioned on page 304. There are three carboxyl groups and one hydroxyl group in the citric acid molecule, the structure of which has been proven by its formation from glycerol.



Citric acid may be obtained from glucose by fermentation with the organism, *Citromycetes pfefferianus*, and this is one of the two main commercial methods for its production. In the other method calcium citrate is made from cull lemons.

Citric acid is used in beverages, especially lemonade, and also in the form of its salts, of which magnesium citrate and ferric ammonium citrate are the most important. The former is sometimes prescribed as a purgative in medicine, and the latter, because of the fact that light reduces ferric iron to ferrous, is employed in the manufacture of blueprint paper.

Higher Hydroxy Acids. There are many hydroxy acids having three or more hydroxyl groups in the molecule. In general, these can be obtained by the oxidation of the sugars, and on that account they are sometimes called sugar acids. Among these acids are some exhibiting an interesting type of stereoisomerism. In such cases the molecule has an odd number of asymmetric carbon atoms and is symmetrical with respect to a bisecting plane. The trihydroxyglutaric acids constitute the simplest example.

There are only four stereoisomeric trihydroxyglutaric acids, namely, XXXI, XXXII, XXXIII, and XXXIV, Figure 21.

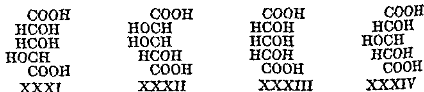


Figure 21 • Stereoisomeric Trihydroxyglutaric Acids

The first two constitute a pair of optical opposites, while XXXIII and XXXIV belong to the indivisible, inactive type. If a plane were passed through either XXXIII or XXXIV so as to bisect the middle carbon atom, the molecule would be divided into two halves that are mirror images of each other. It will be recalled that when this condition holds in the case of the tartaric acids, the molecule is inactive by internal compensation. The same is true here. So, although the central carbon atom is not [illegible] metric carbon atom in the sense of having four different radica[illegible] nevertheless the fact that each of the two like ra[illegible] an asy[illegible] atom makes the configuration of the m[illegible] atom [illegible] an atom is called pseudoasymmetri[illegible]

Number of Stereoisomers. As the number of asymmetric carbon atoms in a molecule increases, the possible number of stereoisomers increases also. Formulas have been worked out by which the number of stereoisomers can be expressed as a function of n, the number of asymmetric (including pseudo-asymmetric) carbon atoms. The formulas shown in Table 61 hold for normal chain compounds.

TABLE 61 | **Number of Stereoisomers**

	ACTIVE	INACTIVE	TOTAL
Unsymmetrical molecules	2^n	0	2^n
Symmetrical molecules			
n is even	2^{n-1}	$2^{\frac{n}{2}-1}$	$2^{\frac{n}{2}-1}(2^{\frac{n}{2}}+1)$
n is odd	$2^{\frac{n-1}{2}}(2^{\frac{n-1}{2}}-1)$	$2^{\frac{n-1}{2}}$	2^{n-1}

PROBLEMS

1. Show the reaction steps involved in preparing the following acids, in inactive form, starting with ethyl alcohol and using only inorganic reagents (including hydrogen cyanide).

a) glycolic acid
b) α-hydroxypropionic acid
c) β-hydroxybutyric acid
d) γ-butyrolactone
e) ε-hydroxycaproic acid
f) malic acid
g) tartaric acid
h) α-hydroxyisobutyric acid
i) α-hydroxy-α-methylbutyric acid
j) α-hydroxy-α-ethylbutyric acid

2. Show the reaction steps involved in preparing the following, in inactive form, from *n*-propyl alcohol, and using only inorganic reagents (including hydrogen cyanide):

a) α-hydroxypropionic acid
b) α-chloropropionic acid
c) α-bromopropionic acid
d) α-propionoxypropionic acid
e) *n*-propyl lactate
f) α-hydroxy-*n*-butyric acid (2 methods)
g) α-hydroxyisobutyric acid
h) crotonic acid
i) α-methylacrylic acid
j) β-hydroxy-*n*-butyric acid

3. Show how to prepare the following from lactic acid:

a) lactide
b) α-bromopropionic acid
c) α-chloropropionic acid
d) ethyl lactate
e) α-acetoxypropionic acid
f) α-propionoxypropionic acid
g) methyl α-acetoxypropionate
h) ethyl α-*n*-butyroxypropionate
i) β-hydroxypropionic acid
j) α,β-dihydroxypropionic acid

4. Show how to prepare the following from γ-butyrolactone:

a) γ-hydroxybutyramide
b) γ-bromobutyramide
c) γ-(2-hydroxyethoxy)-butyric acid
d) ethyl γ-hydroxybutyrate
e) γ-acetoxybutyric acid
f) γ-propionoxybutyric acid

5. [illegible]
isome [illegible]

a) bromoglutaric acids
b) bromoadipic acids
c) dibromosuccinic acids
d) dibromoglutaric acids
e) dibromoadipic acids
f) tribromoglutaric acids
g) tribromoadipic acids
h) dihydroxy-α,β-dimethylsuccinic acids
i) methyl tartrates (mono and diesters)
j) lactyl tartaric acids (monoesters)
k) lactyl tartaric acids (diesters)
l) methyl citrates (all)
m) *sec*-butyl citrates (monoesters)
n) *sec*-butyl citrates (diesters)
o) ethers (noncyclic) from 2 moles of 1,2-propanediol
p) butanediols
q) butanetriols
r) butanetetrols
s) 2,3,4-pentanetriols
t) glycerol α-bromopropionates (mono and diesters)
u) *sec*-butyl ethers of 2,3-butanediol (monoethers)
v) *sec*-butyl ethers of 2,3-butanediol (diethers)

6. Describe a convenient test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) glycolic acid and acetic acid
b) glycolic acid and tartaric acid
c) malic acid and tartaric acid
d) lactic acid and hydracrylic acid
e) tartaric acid and succinic acid
f) α-hydroxybutyric acid and butyric acid
g) γ-butyrolactone and ethyl γ-hydroxybutyrate
h) α-hydroxybutyric acid and α,β-dihydroxybutyric acid
i) α-hydroxybutyric acid and β-hydroxybutyric acid
j) α-hydroxybutyric acid and γ-hydroxybutyric acid

7. If the following compound were the only organic compound available, how could malic acid be best *prepared* from it? Sodium cyanide may be considered to be inorganic.

a) ethanol
b) glycol
c) 1-propanol
d) 1,3-propanediol
e) propionic acid
f) 1,4-butanediol
g) 2,3-butanediol
h) β,γ-dihydroxybutyric acid

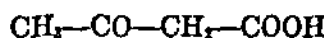
CHAPTER 19

Aldehydic and Ketonic Acids; Syntheses with Ethyl Acetoacetate and Ethyl Malonate

Carboxylic acids which have an oxo group as a second functional group are aldehydic acids when this second group is on the end of a carbon chain, or ketonic acids if it is not at the end. A typical example of an aldehydic acid is succinaldehydic acid, I, and of a ketonic acid is acetoacetic acid, II.



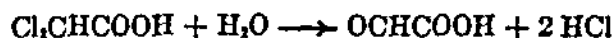
succinaldehydic acid
β-formylpropionic acid
I



β-ketobutyric acid
acetoacetic acid
II

In general these acids show characteristic reactions due to these two functional groups. In addition, other reactions arise from the influence of one group upon the other, or from their combined influence on some other group. The most important of these effects is found in the reactions of ethyl acetoacetate.

Glyoxalic Acid, Glyoxylic Acid, CHO—COOH. This is the simplest oxo acid. It is found in the leaves and unripe fruits of many plants. It disappears during the ripening process. It may be prepared by hydrolysis of dichloroacetic or dibromoacetic acid, or by oxidation of tartaric acid with periodic acid (p. 310).



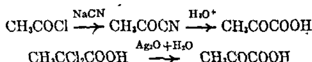
Glyoxalic acid is difficult to obtain pure because of its tendency to polymerize and to undergo dismutation. The latter reaction proceeds slowly in aqueous solution, rapidly under basic conditions. The products are oxalic and glycolic acids.



It crystallizes as a hydrate, which like chloral hydrate (p. 285) is believed to be a dihydroxy compound, $(HO)_2CHCOOH$. This is another example of a strongly negative substituent, in this case the carboxyl group, acting to stabilize a normally unstable compound.

Formylacetic Acid, Malonaldehydic Acid, $CHOCH_2COOH$. The ethyl ester can be obtained in the form of its sodium salt from ethyl formate, ethyl acetate, and sodium ethoxide (p. 323). The ester itself and the acid polymerize rapidly. Higher aldehydic acids also polymerize.

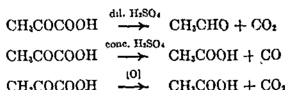
Pyruvic Acid, α-Ketopropionic Acid, Pyroracemic Acid, $CH_3COCOOH$. This is the simplest and most important α-keto acid. The best method of preparation is from tartaric acid, by heating with potassium bisulfate (p. 309). Also it can be obtained from acetyl chloride by the nitrile synthesis, or from α,α-dichloropropionic acid with water and silver oxide.



$$CH_3COCl \xrightarrow{NaCN} CH_3COCN \xrightarrow{H_3O^+} CH_3COCOOH$$

$$CH_3CCl_2COOH \xrightarrow{Ag_2O + H_2O} CH_3COCOOH$$

The stability of the bond joining the carbonyl and carboxyl carbon atoms is decreased by the accumulation of oxygen atoms. When heated with dilute sulfuric acid carbon dioxide is eliminated, and when warmed slightly with concentrated sulfuric acid, carbon monoxide is eliminated. The bond is cleaved by ammoniacal silver solution (reduction to metallic silver) and by other oxidizing agents.



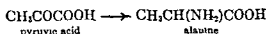
$$CH_3COCOOH \xrightarrow{\text{dil. } H_2SO_4} CH_3CHO + CO_2$$

$$CH_3COCOOH \xrightarrow{\text{conc. } H_2SO_4} CH_3COOH + CO$$

$$CH_3COCOOH \xrightarrow{[O]} CH_3COOH + CO_2$$

These are typical reactions of α-keto acids. A suitable reducing agent (sodium amalgam) reduces pyruvic acid to lactic acid.

Pyruvic acid is important to the biochemist. It is believed to be an intermediate in a number of fermentations of the hexose sugars, for example, those producing ethyl alcohol, lactic acid, propionic acid, and 1-butanol. Also, it is believed to be interconvertible in the animal organism with the amino acid, alanine, and thus is an intermediate in the synthesis and utilization of this acid. In the liver, pyruvic acid is converted to alanine.



$$\underset{\text{pyruvic acid}}{CH_3COCOOH} \longrightarrow \underset{\text{alanine}}{CH_3CH(NH_2)COOH}$$

TABLE 62 **Constants of Some Oxo Acids**

NAME	FORMULA	M.P. °C	B.P. °C	K_a	SOLY. IN WATER
Glyoxylic	$OCHCOOH$			4.7×10^{-4}	misc.
Pyruvic	$CH_3COCOOH$	13.6	165[a]	3.2×10^{-3}	misc.
Acetoacetic	CH_3COCH_2COOH		[b]	1.5×10^{-4}	misc.
Levulinic	$CH_3COCH_2CH_2COOH$	31	245–246	2.5×10^{-5}	v. sol.

[a] Decomposes. [b] Decomposes at 100°; second dissociation constant, 2×10^{-12}.

Acetoacetic Acid, β-Ketobutyric Acid, CH_3COCH_2COOH. This is sometimes called diacetic acid. It is the simplest and most important β-ketonic acid. The acid itself is important in biological oxidation of fatty acids; the ethyl ester is important in synthesis.

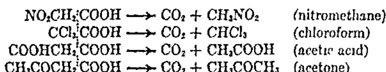
The acid is prepared from the ethyl ester by saponification in dilute aqueous base at room temperature, followed by acidification with sulfuric acid and extraction with ether. On evaporation of ether the acid remains as an oily liquid.

Acetoacetic acid is unstable. When heated it undergoes decarboxylation with formation of acetone.



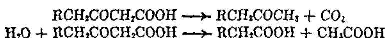
$$CH_3COCH_2COOH \longrightarrow CH_3COCH_3 + CO_2$$

In general, the presence of a negative radical attached to the methyl carbon atom of acetic acid leads to instability. Nitroacetic acid is unstable at room temperature, trichloroacetic acid with alkali undergoes decarboxylation, and malonic acid decarboxylates when heated.



$$NO_2CH_2{\vdots}COOH \longrightarrow CO_2 + CH_3NO_2 \quad \text{(nitromethane)}$$
$$CCl_3{\vdots}COOH \longrightarrow CO_2 + CHCl_3 \quad \text{(chloroform)}$$
$$COOHCH_2{\vdots}COOH \longrightarrow CO_2 + CH_3COOH \quad \text{(acetic acid)}$$
$$CH_3COCH_2{\vdots}COOH \longrightarrow CO_2 + CH_3COCH_3 \quad \text{(acetone)}$$

β-Ketonic acids in general undergo decarboxylation when heated. In the animal organism they undergo scission to two acids, one of them acetic acid.

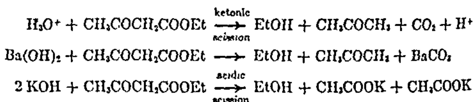


$$RCH_2COCH_2COOH \longrightarrow RCH_2COCH_3 + CO_2$$
$$H_2O + RCH_2COCH_2COOH \longrightarrow RCH_2COOH + CH_3COOH$$

Biological oxidation of fatty acids normally proceeds by degradation of the carbon chain two carbon atoms at a time. This is believed to result from oxidation at the β-carbon atom, forming a β-keto acid, which then undergoes the hydrolysis to acetic acid and another acid, on which the operation can continue. Normally acetoacetic acid would be one of the last intermediates, since all fatty acids of fats are even-numbered carbon compounds. In some pathological cases, *e.g.*, in diabetes, the presence of acetone in the breath or sometimes in the urine is believed to result from acetoacetic acid by the decarboxylation process.

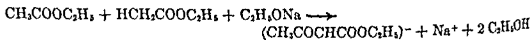
Ethyl Acetoacetate, Acetoacetic Ester, $CH_3COCH_2COOC_2H_5$. This compound is of particular interest as a useful synthetic reagent and as a classical example of the phenomenon of tautomerism. It is a colorless somewhat viscous liquid with a pleasant ethereal odor and decomposes slowly when distilled at atmospheric pressure (see Table 63). It has weakly acidic properties and dissolves in cold dilute aqueous sodium hydroxide, from which it is partly precipitated on the addition of acid soon afterwards. However, it slowly saponifies in this solution to form sodium acetoacetate. The apparent ionization constant, K_a, is about 10^{-11}.

It undergoes two types of decomposition, which are shown also by its homologs, and which are important in connection with acetoacetic ester syntheses. It undergoes the **ketonic scission** (*ketone formation*) when heated with dilute aqueous acids, or even with dilute bases (especially barium hydroxide); it undergoes the **acidic scission** (*acid formation*) when heated with concentrated base.



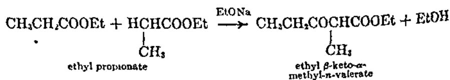
The reactions are not mutually exclusive, for often one is a side reaction to the other.

Ethyl acetoacetate is formed by the action of metallic sodium on anhydrous ethyl acetate containing a little ethyl alcohol, a reaction discovered by Geuther in 1863, or by the action of sodium ethoxide on ethyl acetate free of water and alcohol. In the first case the sodium slowly dissolves with evolution of hydrogen. Evaporation of the mixture leaves behind an impure mixture of sodium ethoxide and a sodium salt of ethyl acetoacetate. When metallic sodium is used the yields usually are better. Decomposition of the reaction mixture with dilute acetic acid gives ethyl acetoacetate.



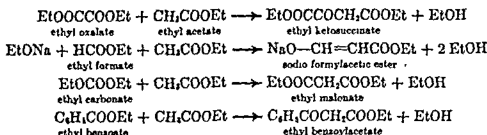
Sodium ethoxide, from the action of metallic sodium on alcohol in ethyl acetate, causes the condensation of two molecules of ethyl acetate by the removal of a molecule of ethyl alcohol.

Claisen Condensation. Acetoacetic ester formation is a *type of condensation* known as the Claisen condensation from the name of the man who carried out extensive investigations on this important synthetic method. Metallic sodium or sodium ethoxide brings about the change at room temperature with a large number of esters having a methylene group, *e.g.*, RCH_2CO_2Et. The reaction always takes place between the carbonyl group of one molecule and the *alpha*-carbon atom of a second molecule. The overall result is the elimination of a molecule of alcohol. Ethyl propionate is a typical case.

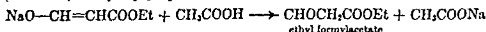


Actually a sodium salt is the product and this can be decomposed by acetic acid or a stronger acid to give the final product. In general it will be assumed that two such steps are involved when only one equation is written to show the condensation reaction. Ethyl isobutyrate does not react. However, it reacts in contact with a much stronger base, for example, sodium triphenylmethyl (Chap 37), even though it does not have a methylene group

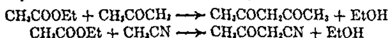
Two different esters can react. If each has a reactive methylene group, mixtures of the four possible products are obtained. If one ester does not have a methylene group, then a single product is often possible. Esters of this type are ethyl oxalate, ethyl formate, ethyl carbonate, and ethyl benzoate. The following are typical reactions.



The product with ethyl formate is stable in the form of the sodium salt, but when the compound, ethyl formylacetate (malonaldehydic ester), is liberated from the salt, it rapidly polymerizes.

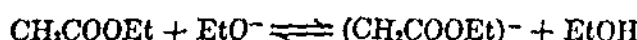


Other compounds having a reactive α-methyl or α-methylene group, for example, ketones and nitriles, may undergo the Claisen condensation with esters. Acetone yields acetylacetone and acetonitrile yields acetylacetonitrile with ethyl acetate. In the last case the yield is low.

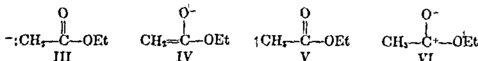


Methyl ketones react preferably at the methyl group, rather than at a methylene group.

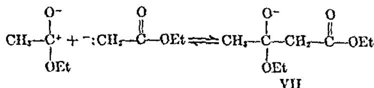
The mechanism of the Claisen condensation has been the subject of numerous investigations. It is believed to resemble, in a general way, the aldol condensation (p. 272). Sodium ethoxide, a very strong base, is able to extract a proton from the ethyl acetate molecule.



The reaction is reversible and, because of the extremely weak acidic character of ethyl acetate, only a small amount of either reactant is believed to be converted. However, the resulting anion of ethyl acetate would be quite reactive. It has two resonance forms, III and IV, and the existence of these two contributes to the stability of the anion. In III the carbon atom carries a formal negative charge and thus is a typical nucleophilic reagent, like other carbanions (p. 86).

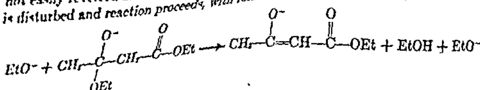


On the other hand, ethyl acetate itself is stabilized by resonance involving the two forms, V and VI. Thus, ethyl acetate, as VI, is an electrophilic reagent. It is believed that reaction proceeds merely by bond formation between the negatively and positively charged carbon atoms, to produce a small amount of the unstable intermediate negative ion, VII.

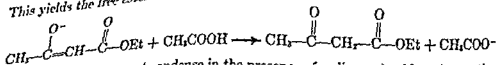


This is the anion of the hemiacetal (ketal) of ethyl acetoacetate. *It is believed to* ... However a strong base is ... double bond ...

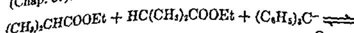
in loss of a molecule of alcohol and ... Thus the equilibrium of the first reaction *not easily reversed under these conditions* ... *is disturbed and reaction proceeds, with formation* of the anion of ethyl acetoacetate.

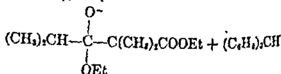


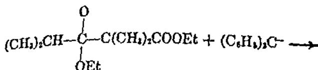
This yields the free ester with acetic or stronger acid.

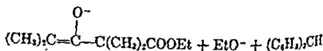


... condense in the presence ... At one time ... However, condensation ... , $(C_6H_5)_3CNa$ (Chap. 37).



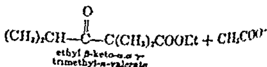






Triphenylmethylsodium is a stronger base than sodium ethoxide and thus promotes the first reaction. Also it is able to extract a proton from the intermediate anion, a change which sodium ethoxide cannot bring about since it is not a strong enough base. Extraction of the proton permits ethoxide ion to leave also, thus giving the anion of ethyl β-keto-α,α,γ-trimethylvalerate. On the addition of a stronger acid the β-ketoester is obtained.





This result is regarded as evidence in favor of the above mechanism of the reaction.

Tautomerism of Ethyl Acetoacetate. The ester acts both as a ketone and as an unsaturated alcohol. By the action of ethyl orthoformate it is converted into the ketal, $CH_3C(OC_2H_5)_2CH_2COOC_2H_5$.

$$CH_3\underset{\substack{\|\\ O}}{C}CH_2COOC_2H_5 + HC(OC_2H_5)_3 \longrightarrow CH_3\text{—}\underset{C_2H_5O\diagup\ \diagdown OC_2H_5}{C}\text{—}CH_2COOC_2H_5 + HCOOC_2H_5$$

This is a characteristic reaction of ketones. On the other hand, rapid reaction in aqueous or alcoholic solution with bromine indicates unsaturation, and the formation of a deep violet-red color with ferric chloride indicates the presence of the hydroxyl group. Thus the ketal reaction points to the ketone structure VIII and the other reactions to the enol structure IX.

$$\underset{\substack{\text{ethyl } \beta\text{-ketobutyrate}\\ \text{keto form}\\ \text{VIII}}}{CH_3\text{—}\overset{\substack{O\\ \|}}{C}\text{—}CH_2\text{—}\overset{\substack{O\\ \|}}{C}\text{—}OC_2H_5} \qquad \underset{\substack{\text{ethyl } \beta\text{-hydroxycrotonate}\\ \text{enol form}\\ \text{IX}}}{CH_3\text{—}\overset{\substack{OH\\ |}}{C}\text{=}CH\text{—}\overset{\substack{O\\ \|}}{C}\text{—}OC_2H_5}$$

In addition, the ability to form a sodium salt by the action of sodium ethoxide was in the past regarded as proof of the enol structure. These contradictions, which intrigued chemists for many years, stimulated extensive investigations. The contradictions were reconciled by the recognition that there exists a dynamic equilibrium between the two forms, so that the compound can react completely as one form or the other and thus show the reactions of both forms. This phenomenon is called **tautomerism** (Gr. *to* + *auto*, the same).

Proof that the ester is an equilibrium mixture of tautomeric forms was obtained in 1911 by K. Meyer, by means of bromine titration. This involves adding a cold standard bromine solution (originally alcoholic bromine) to a cold solution of the ester, immediate removal of excess bromine by addition of some other reagent (phenol, for example) to prevent reaction of bromine with the keto form, adding potassium iodide, and determining the amount of iodine formed.

$$Br_2 + CH_3C(OH)\text{=}CHCOOEt \longrightarrow [CH_3CBr(OH)\cdot CHBrCOOEt]$$
$$[CH_3CBr(OH)\text{—}CHBrCOOEt] \longrightarrow CH_3COCHBrCOOEt + HBr$$
$$2\,HI + \underset{\text{ethyl }\alpha\text{-bromoacetoacetate}}{CH_3COCHBrCOOEt} \longrightarrow \underset{\text{ethyl acetoacetate}}{CH_3COCH_2COOEt} + I_2 + HBr$$

Bromine adds rapidly to the double bond of the enol form, whereas it reacts relatively slowly with the keto form. The resulting addition compound by loss of hydrogen bromide becomes ethyl α-bromoacetoacetate, in which the bromine is easily removed by a mild reducing agent like iodide ion. Meyer showed that acetoacetic ester is a mixture of enol, 7.4 per cent, and ketone 92.6 per cent.

The pure enol and keto forms of acetoacetic ester were isolated by Knorr in 1911. Working at Dry Ice temperature, a solution of acetoacetic ester in ether or ether-hexane, when evaporated at reduced pressure, yielded the keto ester in crystalline form; the sodium salt of ethyl acetoacetate, when carefully

decomposed by dry hydrogen chloride, yielded the enol modification as a liquid. The properties of these two forms differ as shown in Table 63.

TABLE 63 | Properties of Acetoacetic Ester

	M.P. °C	B.P. AT 2 MM. °C	REFRACTIVE INDEX n_D^{10}	DECOLORIZES Br_2	COLOR WITH $FeCl_3$	REACHES EQUILIBRIUM IN
Keto ester	−39	40–41	1.4225	slowly	slow, at −40°	weeks–months
Enol ester	< −78	33	1.4480	rapidly	rapid, at −78°	10–14 days
Equilibrium mixture	−45 to −43	39–40	1.4232	rapidly	rapid	

The isomeric forms when kept in quartz vessels are stable at −78° for a long time, but at room temperature they change slowly to the equilibrium mixture (see Table 63). Ordinary glass increases the rate of change, even at −78°. Many other substances act catalytically, for example, hydrogen chloride gas, tripropylamine vapor, cigarette smoke, and dust. Transferring the enol isomer in impure laboratory air may cause it to change to the equilibrium mixture within a few seconds, whereas in the absence of any catalyst equilibrium is not reached until after 10 to 14 days.

When the tautomeric forms can be isolated as in this case, the phenomenon is called **desmotropy**, and they are called **desmotropic** forms. Some chemists define tautomeric systems as those which, like acetoacetic ester originally, have not been separated into two different compounds.

A more convenient method of obtaining the pure desmotropic forms depends upon careful fractional distillation at reduced pressure. When done through an all quartz apparatus the more volatile enol distils first, then finally the pure ketonic form. When done from a glass boiler through a quartz distilling apparatus, the pure enol is obtained. This is because glass catalyzes the isomerization and quartz does not. Fractionation returns the higher boiling ketonic isomer to the boiler where it undergoes partial enolization, and the enol is slowly distilled out.

The composition of the equilibrium mixture can be approximated also from the physical data, for example, the refractive index. This gives a value of 3 per cent enol, 97 per cent ketone, compared to 7.4 and 92.6, respectively, by bromine titration. From these equilibrium data it is evident that the specific reaction rate of ketonization, *i.e.*, conversion of enol to ketone, is about 12 times the rate of enolization, the reverse reaction.

The position of equilibrium is different in the gaseous state, *viz.*, 46 per cent enol and 54 per cent ketone. Also it is affected by the solvent and is shifted in the direction of the more soluble form. In water the ketonic desmotrope

is the more soluble, and in hexane the enolic isomer is. Equilibrium data are shown in Table 64. These indicate that rates of ketonization and of enolization are affected differently by the solvent. In general, rates of the two reactions increase with a rise in temperature. Rates are also increased by solvents having a hydroxyl group, for example, water and alcohol. Rates decrease on the addition of a hydrocarbon or of a halogenated hydrocarbon. Thus a solvent like water increases the rate of ketonization more than that of enolization, and one like hexane decreases the rate of ketonization more than that of enolization. In hexane the equilibrium is the same as in the gaseous state.

TABLE 64 | Percentage of Enol Form of Acetoacetic Ester in Different Solvents

Solvent	Per cent enol	Solvent	Per cent enol
Water	0.4	Pentanol	13.3
Methanol	6.9	Ether	27.1
Pure compound	7.4	Carbon disulfide	32.4
Ethanol	12.0	Hexane	46.4

Resonance as a Factor in Enolization. In a simple aldehyde or ketone the tendency to form the corresponding enol is so small that sensitive tests fail to show its presence. The equilibrium lies very far over on the side of the oxo compound. This would be expected from the fact that ΔH of enolization in the gas phase is strongly positive, as calculated from bond energies (p. 17).



$$CH_3CHO \longrightarrow CH_2{=}CHOH \quad \Delta H = +14.7 \text{ kcal.}$$
$$CH_3COCH_3 \longrightarrow CH_2{=}C(OH)CH_3 \quad \Delta H = +17.7 \text{ kcal.}$$

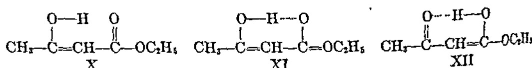
In the liquid phase reaction the values are not greatly different from these. Since ΔF is approximately equal to ΔH in these two reactions, it is evident that the equilibrium constant has an exceeding small value. With change in structure the percentage of enol in an equilibrium mixture may become significant or even quite large, as the data of Table 65 show.

TABLE 65 | Enolization and Structure

NAME	FORMULA	RADICAL	PER CENT ENOL
Methyl ethyl ketone	$CH_3COCH_2CH_3$	CH_3	very low
Acetoacetic ester	$CH_3COCH_2COOC_2H_5$	$COOC_2H_5$	7.4
Acetomalonic ester	$CH_3COCH(COOC_2H_5)_2$	$(COOC_2H_5)_2$	16.8
Acetylacetone	$CH_3COCH_2COCH_3$	$COCH_3$	80.4
Benzoylacetone	$CH_3COCH_2COC_6H_5$	COC_6H_5	98–99
Acetylacetaldehyde	CH_3COCH_2CHO	CHO	>98

It is seen that changing a methyl group of methyl ethyl ketone to the carbethoxy group of ethyl acetoacetate greatly increases the percentage of enol, and that this becomes progressively greater with acetyl, benzoyl, and formyl groups. Thus, one acetyl group alone attached to a carbon atom holding a hydrogen atom does not bring about enolization, but this reaction does take place with one acetyl and one carbethoxy, two acetyl, one acetyl and one benzoyl, or one acetyl and one formyl group.

The enolic form of these compounds is more stable than that of methyl ethyl ketone, because the hydroxyl group is not free but is hydrogen bonded to the other oxygen atom, as shown by X. The greater volatility of the enolic, relative to the ketonic, form of ethyl acetoacetate is explained on this basis, for in general the hydroxyl derivative of a hydrocarbon has a higher boiling point than the keto derivative, for example, isopropyl alcohol, 82°, acetone, 56°. The increased stability of the enol of acetoacetic ester, in comparison to a simple enol, is due in part to the energy of a *hydrogen bond* (usually about 3 kcal., sometimes 5–6 kcal.) and to the resonance energy resulting from the contribution of the three forms, X, XI, and XII, to the structure, in addition to IX (p. 325)



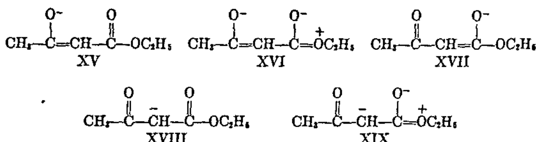
In these cyclic forms the hydrogen atom is bonded to both oxygen atoms. The characteristic infrared band of the hydroxyl group is not present in the infrared absorption spectrum of benzoylacetone (Table 65), although this compound exists almost entirely in the enolic form. This condition has been found in other molecules where the hydrogen atom of the hydroxyl group can form a bond with another oxygen atom, as in *ortho*-nitrophenol (Chap. 33).

Thus the stability of the enolic form of ethyl acetoacetate is increased by these two factors, hydrogen bonding and resonance; and ΔH of enolization, instead of being +18 kcal., is of the order of a few kcal. Since ΔF of enolization is approximately that of ΔH, a measurable equilibrium exists. The enol of acetylacetone relative to the keto isomer is even more stable, for in this case the two resonance forms, XIII and XIV, are equivalent, a condition that leads to greater stability (Chap. 3). In this case ΔF is actually negative.



This explains the fact that this compound is largely enolic. Since ΔH of enolization is 3 kcal. greater for a ketone than for an aldehyde (p. 327), the enol of acetylacetaldehyde would be expected to be more stable than the enol of acetylacetone (Table 65).

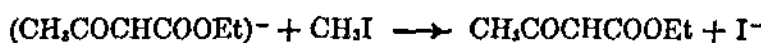
Sodio Acetoacetic Ester. This usually is formed from ethyl acetoacetate by the action of sodium ethoxide in absolute ethyl alcohol. The reaction proceeds well to completion since ethyl acetoacetate is a much stronger acid than ethanol. The acid constants are approximately 10^{-11} and 10^{-20}, respectively. The resulting salt, sodio acetoacetic ester, like other sodium salts, is largely ionic in ionizing solvents excluding alcohols. The ion is stabilized by resonance among five forms, XV to XIX



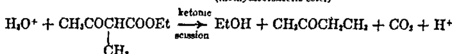
Those in which the carbon atom carries a formal negative charge, XVIII and XIX, have a lower stability than the others, consequently their contribution to the overall structure is small. However from the standpoint of chemical reactivity they are quite important, for the carbon atom is reactive, in this respect resembling other anions with negatively charged carbon atoms. Thus sodio acetoacetic ester is nucleophilic, and tends to react with alkyl halides so as to form a bond with the electrophilic carbon atom of the halide. The negative ion has a greater energy of stabilization due to resonance than has the free ester, since there are more resonance forms. This is an important factor in connection with acidity (Chap. 3).

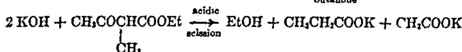
Since the ion is a resonance hybrid of several forms and since on this account the negative charge of the ion is not localized on any one atom, it has become customary to write the ion with the charge outside, thus: $(CH_3COCHCOOEt)^-$. In subsequent equations the anions will be indicated in this way, but it should be noted that reaction proceeds most rapidly at the carbon atom, and in a manner that recalls the way other carbanions attack alkylating agents (p. 110).

Syntheses with Ethyl Acetoacetate; the Acetoacetic Ester Synthesis. The value of ethyl acetoacetate in synthesis depends upon these reactions: (1) formation of the sodium salt; (2) metathesis of this with alkylating agents; (3) the ketonic scission of the resulting product; (4) the acidic scission of the resulting product (p. 322) The products which can be formed are alkyl derivatives of ethyl acetoacetate, alkyl derivatives of acetone, and alkyl derivatives of acetic acid. Methyl iodide is taken as a typical alkylating agent reacting with the anion of ethyl acetoacetate in absolute alcohol.



ethyl methylacetoacetate (methylacetoacetic ester)





Secondary alkyl halides give low yields of an alkylacetoacetic ester, while tertiary give very low yields. In the latter case the main product is an olefin.

A second alkyl radical may be introduced by reaction of an alkylating agent

with the sodium salt of ethyl methylacetoacetate. It may be a different radical from the first. However only primary alkyl radicals give satisfactory yields.

$$CH_3COCH(CH_3)COOEt + EtO^- \longrightarrow (CH_3COC(CH_3)COOEt)^- + EtOH$$

$$(CH_3COC(CH_3)COOEt)^- + \underset{\text{1-bromobutane}}{BrC_4H_9} \longrightarrow \underset{\substack{\text{ethyl methyl-}n\text{-butylacetoacetate} \\ \text{(methyl-}n\text{-butylacetoacetic ester)}}}{CH_3COC(CH_3)(C_4H_9)COOEt} + Br^-$$

$$H_3O^+ + CH_3COC(CH_3)(C_4H_9)COOEt \xrightarrow[\text{scission}]{\text{ketonic}} EtOH + \underset{\text{3-methyl-2-heptanone}}{C_4H_9CH(CH_3)COCH_3} + CO_2 + H^+$$

$$2\,KOH + CH_3COC(CH_3)(C_4H_9)COOEt \xrightarrow[\text{scission}]{\text{acidic}} EtOH + \underset{\substack{\text{potassium} \\ \alpha\text{-methylcaproate}}}{C_4H_9CH(CH_3)COOK} + CH_3COOK$$

With *n*-butyl bromide the first reaction product is a dialkylated acetoacetic ester having one methyl and one butyl radical. From this the ketonic hydrolysis gives a dialkylated acetone (both alkyl radicals on the same carbon atom), and the acidic hydrolysis gives the salt of a dialkylated acetic acid. Thus the four types of products obtainable from ethyl acetoacetate, in addition to esters themselves, are monoalkyl and dialkyl acetones, monoalkyl and dialkyl acetic acids, RCH_2COCH_3, $RR'CHCOCH_3$, RCH_2COOH, and $RR'CHCOOH$, respectively. Here R and R′ may be the same radical or different radicals.

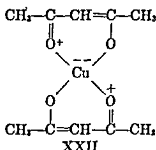
Reagents similar to alkyl halides may be used, that is, those having reactive halogen, for example, allyl halides, $CH_2{=}CHCH_2X$; α-chloroethers, RCH_2OCH_2Cl; α-bromoketones, $RCHBrCOCH_3$; esters of α-bromacids, $RCHBrCOOR'$; and acyl halides, RCH_2COX. However, acyl halides may react to give so-called oxygen esters, as well as carbon derivatives. For example, acetyl chloride yields two compounds, ethyl diacetoacetate, XX, the normal reaction product, and ethyl β-acetoxycrotonate, XXI, the oxygen ester.

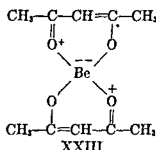
$$\underset{\text{XX}}{CH_3COCH(COCH_3)COOEt} \qquad \underset{\text{XXI}}{CH_3C(OCOCH_3){=}CHCOOEt}$$

A large number of β-keto esters can be obtained by methods described in this chapter. They are: (1) $RCH_2COCHRCOOEt$, from the Claisen condensation, (2) $CH_3COCHRCOOEt$, and (3) $CH_3COCRR'COOEt$, from acetoacetic ester.

Chelation Compounds. Acetylacetone reacts with many metallic hydroxides, carbonates, or acetates in aqueous or alcoholic solution to form metallic compounds. Typical of these are (1) the cupric compound, XXII,

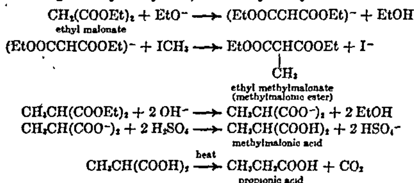
which separates from acetic acid solution as a blue precipitate and is soluble in chloroform with a deep blue color; and (2) the beryllium salt, XXIII, which melts at 108°, boils at 270°, sublimes slowly at 100°, is readily soluble in many organic solvents, *i.e.*, alcohol and ether, and is only slightly soluble in water. The low boiling point and the solubility in organic solvents indicates a lack of saltlike nature. These are characteristic reactions of β-diketones.





In these compounds the metal atom has replaced two hydrogen atoms of two molecules of enol and has formed coordination bonds with the two carbonyl oxygen atoms so as to have the stable coordination number of 4. This tendency of an element to form coordination bonds, usually with the production of a ring, is called chelation. Similar to this is the function of a hydrogen atom in the enol form of acetoacetic ester and of β-diketones.

Syntheses with Ethyl Malonate; Malonic Ester Synthesis. This synthetic method is described here rather than earlier because it is quite similar to the acetoacetic ester synthesis. The ester forms a sodium salt by the action of sodium ethoxide and this reacts with alkylating agents (alkyl halides, alkyl sulfates) to form alkyl derivatives of ethyl malonate. The acids of these are alkylmalonic acids, which, like malonic acid, easily decarboxylate when heated to yield alkylacetic acids (p. 191). The reaction with methyl iodide is typical of reactions with primary alkyl bromides and iodides. Here also tertiary halides give very low yields, secondary low yields.



$$\underset{\text{ethyl malonate}}{CH_2(COOEt)_2} + EtO^- \longrightarrow (EtOOCCHCOOEt)^- + EtOH$$

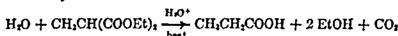
$$(EtOOCCHCOOEt)^- + ICH_3 \longrightarrow \underset{\substack{\text{ethyl methylmalonate} \\ \text{(methylmalonic ester)}}}{\underset{CH_3}{EtOOC\overset{|}{C}HCOOEt}} + I^-$$

$$CH_3CH(COOEt)_2 + 2\,OH^- \longrightarrow CH_3CH(COO^-)_2 + 2\,EtOH$$

$$CH_3CH(COO^-)_2 + 2\,H_2SO_4 \longrightarrow \underset{\text{methylmalonic acid}}{CH_3CH(COOH)_2} + 2\,HSO_4^-$$

$$CH_3CH(COOH)_2 \xrightarrow{\text{heat}} \underset{\text{propionic acid}}{CH_3CH_2COOH} + CO_2$$

Instead of the two steps of saponification and acidification, the ester can be heated with aqueous sulfuric acid to bring about the two reactions of hydrolysis and decarboxylation.



$$H_2O + CH_3CH(COOEt)_2 \xrightarrow[\text{heat}]{H_3O^+} CH_3CH_2COOH + 2\,EtOH + CO_2$$

A second alkyl group, if primary, can be introduced into the molecule of ethyl methylmalonate. This may be a similar or different radical. The reaction with *n*-butyl bromide is typical.

$$CH_3CH(COOEt)_2 + EtO^- \longrightarrow [CH_3C(COOEt)_2]^- + EtOH$$

$$[CH_3C(COOEt)_2]^- + \underset{n\text{-butyl bromide}}{BrC_4H_9} \longrightarrow \underset{\substack{\text{ethyl methyl-}n\text{-butylmalonate} \\ (\text{methyl-}n\text{-butylmalonic ester})}}{C_4H_9{-}\underset{\displaystyle CH_3}{\underset{|}{C}}(COOEt)_2} + I^-$$

$$C_4H_9{-}\underset{\displaystyle CH_3}{\underset{|}{C}}(COOEt)_2 \xrightarrow[\text{heat}]{H_3O^+} \underset{\alpha\text{-methylcaproic acid}}{CH_3CH_2CH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCOOH} + 2\,EtOH + CO_2$$

The products that can be obtained by the malonic ester synthesis are, in addition to the alkylmalonic esters, monoalkyl and dialkyl malonic acids, and monoalkyl and dialkyl acetic acids, $RCH(COOH)_2$, $RR'C(COOH)_2$, RCH_2COOH, and $RR'CHCOOH$, respectively. Here R and R′ may be the same radical or different radicals.

Other types of halogen compounds may react with sodiomalonic ester, for example, allyl halides, α-bromoketones, α-chloroethers, esters of α-bromo-acids, and acyl halides.

Cyclic compounds may be prepared from malonic ester by the use of α,ω-dibromides, in particular ethylene bromide and trimethylene bromide.

$$(EtOOCCHCOOEt)^- + BrCH_2CH_2Br \longrightarrow EtOOC\underset{\displaystyle CH_2CH_2Br}{\underset{|}{C}}HCOOEt + Br^-$$

$$BrCH_2CH_2CH(COOEt)_2 + EtO^- \longrightarrow \underset{\substack{\text{ethyl cyclopropane-} \\ 1,1\text{-dicarboxylate}}}{\begin{matrix} CH_2 & & COOEt \\ | & C & \\ CH_2 & & COOEt \end{matrix}} + Br^- + EtOH$$

The intermediate compound formed at the first step is not isolated. The main difficulty is the reaction of the dibromide with two molecules of ester, for this leads to the formation of linear polymers. This is more important with higher α,ω-dibromides.

The anion of malonic ester, formed by the action of sodium ethoxide or of a stronger base (sodamide) resembles the anion of acetoacetic ester in being a resonance hybrid. *There are seven forms, and in three of these the carbon* atom carries a formal negative charge. Since the formal negative charge is not localized on any one atom, it is convenient in this case also to write the anion with the charge outside, thus: $[CH(COOEt)_2]^-$. In general, reaction proceeds so that the alkyl radical becomes attached to the carbon atom of the anion.

Malonic ester itself, although it forms a sodium salt, appears to be almost completely ketonic, for it gives negative test for enol (color with ferric chlo-

ride). However, infrared absorption spectra show the presence of the hydroxyl group. Two carbethoxy groups attached to one methylene group produce only slight enolization. It will be noted from Table 65 that one carbethoxy and one acetyl group are not as effective as two acetyl groups.

PROBLEMS

1. What compound would be expected to be the principal product when acetic acid is added to the following, after having stood for some time with sodium ethoxide in absolute ethanol? Write equations for any reactions and name the product.

a) methyl propionate
b) ethyl formate
c) ethyl *n*-butyrate
d) ethyl isovalerate
e) ethyl malonate
f) ethyl acetoacetate
g) ethyl hexoate
h) ethyl formate and ethyl propionate
i) ethyl oxalate and ethyl propionate
j) ethyl oxalate and acetone
k) ethyl *n*-butyrate and acetone
l) ethyl *n*-butyrate and ethyl formate
m) ethyl *n*-butyrate and ethyl malonate
n) ethyl oxalate and methyl-*n*-propylketone
o) ethyl oxalate and methylisopropylketone
p) ethyl acetate and ethyl isobutyrate
q) ethyl acetate and methylethylketone
r) ethyl oxalate and methyl-*tert*-butylketone

2. Write equations for preparation of the following in a Claisen type of reaction. Name the compound.

a) $CH_3CH_2CH_2COCH(C_2H_5)COOEt$
b) $EtOOC—COCH(CH_3)COOEt$
c) $CH_3COCOCH(C_2H_5)COOEt$
d) $C_6H_5COCH(CH_3)COOEt$
e) $EtOOC—CH(CH_2CH_3)COOEt$
f) $CH_3CH_2CH_2CH_2COCH(CH_3)COOEt$
g) $CH_3CH_2CH(COOEt)CHO$
h) $CH_3COCOCH(CH_3)COOEt$
i) $EtOOC—COCH(C_2H_5)COOEt$
j) $EtOOC—CH(CHO)CH_2COOEt$
k) $CH_3CH_2COCH_2COCH_3$
l) $CH_3CH_2CH_2COCH_2COCH_3$
m) $C_6H_5COCH(C_2H_5)COOEt$
n) $C_6H_5COCH_2COCH_3$

3. Show how the following may be prepared, starting with acetoacetic ester and using any desired compounds:

a) *n*-caproic acid
b) isocaproic acid
c) heptanoic acid
d) α-methyl-*n*-butyric acid
e) α-ethyl-*n*-butyric acid
f) α-methyl-*n*-caproic acid
g) β-methyl-*n*-caproic acid
h) γ-methyl-*n*-caproic acid
i) 2-ethylheptanoic acid
j) 3-ethylheptanoic acid
k) α-methyl-β-hydroxy-*n*-butyric acid
l) α-ethylcrotonic acid
m) 4-pentenoic acid
n) γ-keto-*n*-valeric acid
o) methylsuccinic acid
p) suberic acid

4. Show how the following may be prepared, starting with acetoacetic ester and using any desired compounds.

a) 2-pentanone
b) 3-methyl-2-butanone
c) 4-methyl-2-pentanone
d) 2-hexanone
e) 2-heptanone
f) 4-heptanone
g) 3-pentanol
h) 2-octanone
i) 5-methyl-2-hexanol
j) α-n-propyl-β-hydroxy-n-butyric acid

5. Show how the following may be prepared, starting with malonic ester and using any desired compounds.

a) *n*-propylmalonic acid
b) di-*n*-propylmalonic acid
c) ethyl isoamylmalonate
d) ethyl isopropylmalonate
e) ethyl methyl-*n*-butylmalonate
f) ethyl methyl-isopropylmalonate
g) 4,4-dicarboxy-1-butene
h) 1,1-dicarboxycyclobutane
i) di-*n*-butylmalonic acid
j) isovaleric acid
k) hexanoic acid
l) 2-methylheptanoic acid
m) 3-methylheptanoic acid
n) 4-methylheptanoic acid
o) 5-methylheptanoic acid
p) 6-methylheptanoic acid
q) α,γ-dimethylvaleric acid
r) α,β-diethylvaleric acid
s) β-methoxypropionic acid
t) β-methyl-γ-keto-*n*-valeric acid

6. Having ethyl alcohol, ethyl acetoacetate, and ethyl malonate as the only organic compounds, show the reaction steps involved in a practical laboratory preparation of:

a) *n*-butyric acid
b) 2-pentanol
c) 2-acetoxypentane
d) α-ethyl-*n*-butyric acid
e) 3-ethyl-2-pentanone
f) β-hydroxy-α-ethyl-*n*-butyric acid
g) ethyl α-carbethoxycrotonate
h) ethyl 2-carbethoxy-2,4-hexadienoate
i) *n*-pentane
j) 3-ethylpentane
k) 2,5-hexanedione
l) succinic acid
m) γ-keto-*n*-valeric acid
n) γ-valerolactone
o) 4-heptanone
p) *n*-heptane

7. Describe a convenient test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

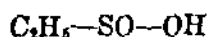
a) lactic acid and pyruvic acid
b) ethyl acetate and ethyl acetoacetate
c) ethyl ethylacetoacetate and ethyl diethylacetoacetate
d) ethyl acetoacetate and ethyl malonate
e) ethyl acetoacetate and acetylacetone
f) ethyl methylacetoacetate and ethyl dimethylacetoacetate
g) ethyl β-ketobutyrate and ethyl β-hydroxybutyrate
h) ethyl malonate and ethyl ethylmalonate
i) ethyl butyrate and ethyl α-ketobutyrate
j) ethyl α-ketobutyrate and ethyl β-ketobutyrate

CHAPTER 20

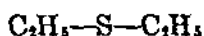
Organic Compounds of Sulfur

There are two main groups of sulfur compounds, in addition to esters of sulfur acids (Chap. 15). These are (1) thio compounds, where a sulfur atom replaces an oxygen atom of an alcohol, ether, acid, etc., and (2) compounds in which the sulfur is in a higher oxidation state than in a thio compound. Thio compounds may be regarded as derivatives of hydrogen sulfide, for in them either one or both of the sulfur-to-hydrogen bonds are replaced by sulfur-to-carbon bonds. Thus the oxidation state of sulfur in a thio compound can be considered to be the same as in hydrogen sulfide. Typical thio compounds are ethanethiol (thioethanol), ethyl mercaptan, I, and ethyl sulfide (thioether), IV. Typical oxidation products of these are ethanesulfinic acid, II, ethanesulfonic acid, III, ethyl sulfoxide, V and ethyl sulfone, VI. The first oxidation product of ethanethiol is ethyl disulfide, VII. Intermediate between I and II are the sulfenic acids, R—S—OH.


I

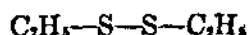

II


III


IV


V


VI


VII

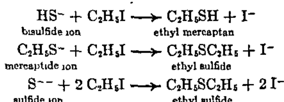
Nomenclature. In the I.U.C. system compounds are named as derivatives of hydrocarbons: I is ethanethiol; II is ethanesulfinic acid; III is ethanesulfonic acid; IV is ethylthioethane; V is ethylsulfinylethane; VI is ethylsulfonylethane; and VII is ethyldithioethane. Other names are given above.

THIO COMPOUNDS

The two simplest types of thio compounds are the thioalcohols (mercaptans), RSH, corresponding to the alcohols, ROH, and the thioethers (sulfides), R_2S, corresponding to the ethers, R_2O. Other types are thioacids and thioesters. Thioaldehydes and thioketones undergo polymerization.

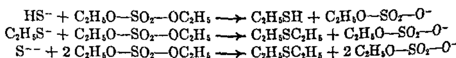
Preparation of Thioalcohols and Thioethers. Usually these are prepared similarly to the alcohols and ethers (first three methods). The ethyl compounds are taken as typical examples.

1. *From an alkyl halide and a sodium (or potassium) salt of hydrogen sulfide or of a thioalcohol.* The reaction usually is carried out in alcoholic solution.

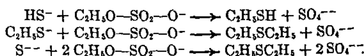


The second reaction is similar to the Williamson synthesis of ethers.

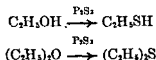
2. *From an alkyl sulfate and a salt, as above.*



3. *From a metallic alkyl sulfate and a salt, as above.* The reaction is carried out in aqueous solution, in which both reactants are soluble.



4. *From the corresponding oxygen compounds, by replacing oxygen with sulfur.* This may be accomplished, usually in low yield, by heating with "phosphorus trisulfide," the product obtained by heating 2 parts of phosphorus with 3 parts of sulfur.



An important industrial method for the production of mercaptans involves passage of alcohol vapor and hydrogen sulfide over a hot dehydrating catalyst, for example, thorium oxide, at 360 to 380°.



Properties of the Mercaptans and Sulfides. These are volatile compounds, the mercaptans boiling below the corresponding alcohols and the sulfides above the corresponding ethers. The lower mercaptans have vile, penetrating odors of such intensity that they can be detected at very low concentrations, that of ethyl mercaptan being observable in a dilution of 1 part in 100,000,000. The objectionable odor in the secretion of the skunk is butyl mercaptan. The odors of the higher mercaptans are much less disagreeable and may be even pleasant (nonyl mercaptan). The unpleasant smell of gasoline and kerosene is believed to be due to sulfur compounds, chiefly mercaptans. As ordinarily prepared, the odors of the sulfides are disagreeable but

are ethereal when pure. In Table 66 the physical constants show how the sulfur atom affects the properties of compounds.

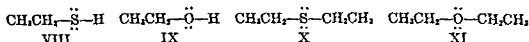
TABLE 66 **Physical Constants of Some Simple Oxygen and Sulfur Compounds**

COMPOUND	M.P. °C	B.P. °C	DENSITY	K_a	SOL. IN WATER G./100 G.	DIELECTRIC CONSTANT
HOH	0	100	0.998	1.8×10^{-16}		78.5
C_2H_5OH	−117	78.5	.789	7.3×10^{-20}	misc.	24.3
$(C_2H_5)_2O$	−116	34.5	.714		7	4.3
HSH	−82.9	−60.2	.96[a]	5.7×10^{-8}	0.44	9.0[b]
C_2H_5SH	−121	34.7	.840	3×10^{-11}	s sol.	6.9
$(C_2H_5)_2S$	−102	91.6	.837		insol.	5.7

[a] At −60°. [b] At −78°

Water is a polar liquid with a high dielectric constant, but hydrogen sulfide has only weakly polar properties, as shown by the relatively low melting point, boiling point, and dielectric constant. As an acid, however, it is stronger than water. Whereas the boiling point of ethyl alcohol is lower than that of water in spite of its greater molecular weight, that of ethyl mercaptan is higher than hydrogen sulfide because of its greater molecular weight. This is because hydrogen bonding is negligible in the sulfur compounds, is considerable in alcohol, and is even more extensive in water. Thus hydrogen bonding may outweigh the effect of a smaller molecular weight (Table 13, p. 31). For the same reasons ethyl ether boils lower than ethyl alcohol. Comparing the two nonpolar liquids, ethyl ether and ethyl sulfide, the latter boils higher because of its greater molecular weight.

Structures of Mercaptans and Sulfides. The methods of preparation indicate that the structures are similar to those of the corresponding oxygen compounds. Thus ethyl mercaptan, VIII, is similar to ethyl alcohol, IX; and ethyl sulfide, X, is similar to ethyl ether, XI.



Reactions of Mercaptans (Thioalcohols). Mercaptans in their chemical behavior strongly resemble alcohols. Ethyl mercaptan will be taken as a typical member of this group.

1. *Mercaptans are weak acids*, ionizing in water solution to give positive hydrogen and negative mercaptide ions.



Ethyl mercaptan is soluble in aqueous solutions of the strong bases because of salt formation, and from these solutions the addition of ions of heavy metals such as mercuric or lead ions throws down insoluble salts.

$$C_2H_5SH + NaOH \rightleftharpoons C_2H_5SNa + H_2O$$
$$2\,C_2H_5SNa + HgCl_2 \longrightarrow (C_2H_5S)_2Hg + 2\,NaCl$$
$$2\,C_2H_5SNa + PbCl_2 \longrightarrow (C_2H_5S)_2Pb + 2\,NaCl$$

The name mercaptan comes from the fact that it combines with mercury (L. *corpus mercurium captans*). When attempt is made to isolate the sodium salt by evaporation, the uncombined mercaptan distils out and the reaction reverses. The sodium salt may be obtained by adding metallic sodium to an ether solution of the mercaptan.

2. *Mercaptans form thioesters with acids.*

$$CH_3COOH + HSC_2H_5 \longrightarrow CH_3COSC_2H_5 + H_2O$$

This reaction is of theoretical interest because it indicates that in esterification the hydroxyl group comes from the acid. Since the resulting ester is a mixed anhydride and one of the reactants, the mercaptan, is a stronger acid than alcohol, the reaction does not proceed as far as in the case of ethyl acetate, for at equilibrium less thioester is formed.

3. *Mercaptans form thioesters with acid chlorides.*

$$CH_3COCl + HSC_2H_5 \longrightarrow CH_3COSC_2H_5 + HCl$$

4. *Mercaptans form mercaptals with aldehydes and mercaptols with ketones;* it will be recalled that alcohols react with aldehydes (in the presence of an acid catalyst) to form acetals (p. 266).

$$\underset{\displaystyle CH_3}{\overset{|}{CHO}} + 2\,HSC_2H_5 \longrightarrow C_2H_5S{-}\underset{\displaystyle CH_3}{\overset{|}{CH}}{-}SC_2H_5 + H_2O$$

mercaptal

$$(H_3C)(CH_3)CO + 2\,HSC_2H_5 \longrightarrow C_2H_5S{-}C(H_3C)(CH_3){-}SC_2H_5 + H_2O$$

mercaptol

The preparation of a mercaptol is one step in the manufacture of a number of important sleep-producing drugs, which are obtained by oxidation of a mercaptol.

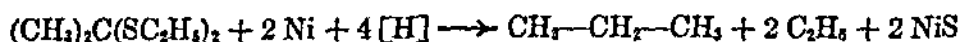
$$C_2H_5{-}S{-}C(H_3C)(CH_3){-}S{-}C_2H_5 + 4[O] \longrightarrow C_2H_5{-}SO_2{-}C(H_3C)(CH_3){-}SO_2{-}C_2H_5$$

mercaptol → sulfonal

Sulfonal is a well-known soporific of this type.

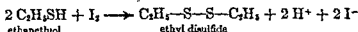
Mercaptals and mercaptols are intermediates for carrying out the reduction of aldehydes and ketones to hydrocarbons. The reducing agent is Raney nickel catalyst. This carries adsorbed hydrogen. Addition of hydrochloric

acid to the residue causes the evolution of hydrogen sulfide. The reduction occurs in good yield by the scission of carbon-to-sulfur bonds.



$$(CH_3)_2C(SC_2H_5)_2 + 2\,Ni + 4\,[H] \longrightarrow CH_3{-}CH_2{-}CH_3 + 2\,C_2H_6 + 2\,NiS$$

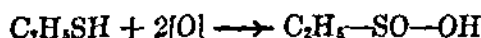
5. *Mercaptans undergo oxidation.* Mild oxidizing agents convert them to disulfides. The reaction with iodine is especially useful for analysis.



$$\underset{\text{ethanethiol}}{2\,C_2H_5SH} + I_2 \longrightarrow \underset{\text{ethyl disulfide}}{C_2H_5{-}S{-}S{-}C_2H_5} + 2\,H^+ + 2\,I^-$$

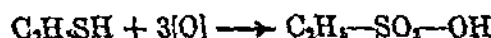
The reaction is reversible, but dilution so favors the forward reaction that it is essentially quantitative.

Stronger oxidizing agents, for example, nitric acid, convert thiols to sulfinic acids.



$$C_2H_5SH + 2[O] \longrightarrow C_2H_5{-}SO{-}OH$$

The oxidation can be carried to the sulfonic acid stage by the action of still stronger oxidizing agents, for example potassium permanganate, hydrogen peroxide, concentrated or fuming nitric acid.

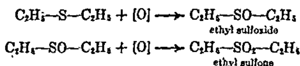


$$C_2H_5SH + 3[O] \longrightarrow C_2H_5{-}SO_2{-}OH$$

Useful in mercuric poisoning is 1-propanol-2,3-dithiol (propanol dimercaptan), BAL (British antilewisite), which on injection removes mercuric salts by forming a stable mercuric derivative.

Reactions of Sulfides (Thioethers). The two important types of reaction are oxidation and coordination.

1. *Oxidation.* By controlled oxidation they are converted to sulfoxides, and finally to sulfones.

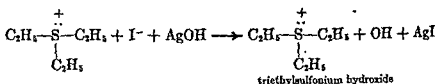


$$C_2H_5{-}S{-}C_2H_5 + [O] \longrightarrow \underset{\text{ethyl sulfoxide}}{C_2H_5{-}SO{-}C_2H_5}$$

$$C_2H_5{-}SO{-}C_2H_5 + [O] \longrightarrow \underset{\text{ethyl sulfone}}{C_2H_5{-}SO_2{-}C_2H_5}$$

2. *Coordination.* Sulfides form addition compounds with salts of some of the heavy metals, for example mercuric chloride and platinum chloride; also with bromine and with alkyl halides. Some typical compounds are: $(C_2H_5)_2S \cdot HgCl_2$, $(C_2H_5)_2S \cdot 2\,HgCl_2$ (with excess $HgCl_2$), $(C_2H_5)_2S \cdot PtCl_2$, $PtCl_2 \cdot 2\,(C_2H_5)_2S$ (with excess $(C_2H_5)_2S$), $(C_2H_5)_2S \cdot Br_2$, and $(C_2H_5)_3SI$. In these compounds a coordination bond has been formed between the sulfur atom and an atom of the reagent, usually the more electropositive atom. Sulfur is the donor element. When combination is with mercury, platinum, or other metallic ion which forms stable coordination bonds, the compounds are definitely covalent, usually soluble in organic solvents and insoluble in water.

Sulfonium Bases. When silver oxide is added to an aqueous solution of triethylsulfonium iodide, silver iodide is precipitated and the solution becomes strongly basic, owing to the formation of triethylsulfonium hydroxide.



On evaporation of the solvent the base is obtained as a crystalline solid. It is a strong base, comparable to sodium hydroxide in strength. It is readily soluble in water and its aqueous solution readily absorbs carbon dioxide from the air.

The strongly basic character of sulfonium bases is easily understood in terms of the Lewis theory of molecular structure. In ethyl sulfide the sulfur atom has a complete octet of electrons. The attachment of the third ethyl radical from ethyl iodide is made as positive ethyl radical to an unshared electron pair of the sulfur atom. This produces the positive triethylsulfonium ion. The iodine atom becomes iodide ion. For a covalent bond to exist between sulfur and iodine, either the sulfur atom or the iodine atom would have to expand its octet. Although this occurs in some cases, sulfur hexafluoride, SF_6, for example, there is no necessity of it here, since each atom already has a complete octet of electrons. Thus the bond is ionic in triethylsulfonium iodide, and also in triethylsulfonium hydroxide. This is a quite satisfactory explanation of the strongly basic character of sulfonium bases. The important deduction can be drawn from this, that the sulfur atom does not expand its octet to form a covalent bond with a negative ion.

Optical isomerism has been observed in the case of sulfonium compounds. In order for optical isomers to exist the molecule cannot have a plane of symmetry. Thus the sulfur atom in the cation cannot be coplanar with the three atoms to which it is attached. It may be pictured as being located at the center of a tetrahedron whose apex is occupied by the unshared electron pair and whose other three vertices are occupied by the three carbon atoms of the alkyl groups, XII.

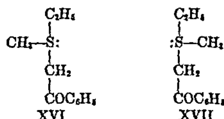


Figure 22 · Projection of an Optically Active Sulfonium Ion

The projection of the three-dimensional model onto a plane surface is shown through the steps, XII to XV, Figure 22. In XIII bonds are drawn from the sulfur atom to three corners at which atoms are attached, in XIV the edges of the tetrahedron are omitted, and in XV the model is flattened onto a plane surface. In XIV it is evident that the three bonds to sulfur are arranged as in a pyramid. The sulfur atom is essentially an asymmetric sulfur atom, in this respect resembling an asymmetric carbon atom (p. 299). The case of

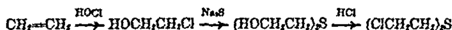
the asymmetry of the molecule is the unshared electron pair, which in essence occupies one corner of the tetrahedron. It is not essential that XII represent a regular tetrahedron. Quite probably it is a distorted tetrahedron. So long as the sulfur atom is not coplanar with the carbon atoms attached to it, stereoisomerism is possible. The limitation on the use of a projection formula applies here, namely, nonremovability from the plane on which it is written.

One of the first sulfonium bases to be resolved was methylethylphenacylsulfonium hydroxide, by means of its salt with (+)-bromocamphoric acid. The two stereochemical forms of the ion are shown as XVI and XVII.



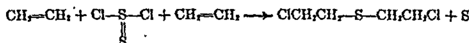
It is evident that these are not superposable, and that they are related to each other as object and mirror image. This is the condition characteristic of optical isomerism (p. 301). Thus the Lewis structure of sulfonium compounds accounts for the strongly basic nature of the hydroxides and also for the possibility of optical isomerism.

Mustard Gas, β,β'-Dichloroethyl Sulfide, $(ClCH_2CH_2)_2S$. This compound was employed more extensively as a poison "gas" during World War I than any other organic compound. Actually it is not a gas but a high boiling liquid (217°), which because of its low vapor pressure remains on the ground for a long period of time. Because of its low solubility in water (0.05 g./100 ml.) it may persist for months under water, which has a lower density than the "gas" (1.279). Not only the liquid but even the vapor produces severe burns upon the skin and mucous membranes, and its effect when inhaled is especially pronounced. The Germans, who introduced its use, prepared it from ethylene through several steps.



$$CH_2{=}CH_2 \xrightarrow{HOCl} HOCH_2CH_2Cl \xrightarrow{Na_2S} (HOCH_2CH_2)_2S \xrightarrow{HCl} (ClCH_2CH_2)_2S$$

The Americans and English developed the much simpler method of passing ethylene into sulfur monochloride.



$$CH_2{=}CH_2 + Cl{-}\underset{\underset{S}{\|}}{S}{-}Cl + CH_2{=}CH_2 \longrightarrow ClCH_2CH_2{-}S{-}CH_2CH_2Cl + S$$

The extra sulfur usually was left in the product since it did not change the toxicity.

[illegible]

oxidize it through the sulfoxide to the sulfone.



$$(ClCH_2CH_2)SCl_2 \longleftarrow (ClCH_2CH_2)_2S \longrightarrow (ClCH_2CH_2)_2SO \longrightarrow (ClCH_2CH_2)_2SO_2$$

Since the dichloride and the oxides are nontoxic, the reagents above may be used to destroy mustard gas. The toxic effects are thought to be due in part to the fact that

it passes with ease into the body tissues where hydrochloric acid is formed by hydrolysis. It is insidious because there is no immediate effect from it. Of those who succumbed, 62 per cent died more than five days after exposure to the gas. It is called mustard gas because of a fancied resemblance to the odor of mustard.

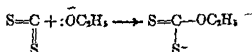
OTHER THIO DERIVATIVES

Thioacids. *Thioacetic acids.* Theoretically three thioacetic acids are possible, *viz.*, thiolacetic acid, CH_3COSH, thionacetic acid, CH_3CSOH, and dithioacetic acid, CH_3CSSH. Although derivatives of all three are known, there is but one monothioacid. Thioacetic acid is of some interest because when esterified with an alcohol, hydrogen sulfide is formed.

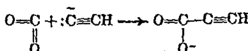


The hydrogen atom comes from the alcohol, not from the acid. The thiol acid is obtained from acetic acid by heating it with phosphorus pentasulfide.

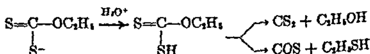
Dithiocarbonic acid; xanthic acid. When carbon disulfide is added to a mixture of an alcohol and a concentrated solution of sodium hydroxide, or to a solution of sodium ethoxide in alcohol, sodium xanthate (sodium ethyl xanthate) is formed rather rapidly.



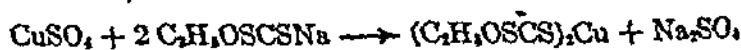
This reaction resembles the reaction of carbon dioxide with nucleophilic reagents such as acetylide ion, Grignard reagents, etc.

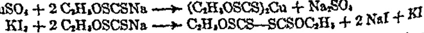


Xanthic Acid is the monoethyl ester of the hypothetical dithiocarbonic acid, HSCSOH. It is unstable and slowly decomposes to carbon disulfide, alcohol, carbon oxysulfide, and mercaptan when liberated from the sodium salt by the addition of a stronger acid.



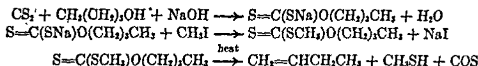
Yellow copper xanthate (Gr. *xanthos*, yellow) is formed on the addition of cupric ions to xanthate ions, and dixanthic acid is precipitated when triiodide ion is added.





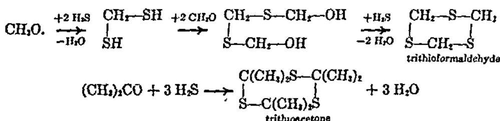
Many xanthates of higher alcohols are known. Some of these, for example, *n*-butyl xanthate, are used in the mining industry as flotation agents, for often they permit selective flotation of different minerals. Cellulose xanthate is important in the manufacture of rayon (Chap. 42). Xanthates often replace carbon disulfide as earth fumigants in vineyards.

A synthetic method for the preparation of olefins involves heating the corresponding alkyl methyl xanthate. This is prepared by the action of methyl iodide on the corresponding sodium alkyl xanthate (Chugaev).



On heating, the methyl *n*-butyl xanthate yields 1-butene, methyl mercaptan, and carbon oxysulfide. The method has the advantage that the olefin formed is the expected product, not a rearranged one, and is especially useful for the preparation of highly branched olefins, some of which are difficult to prepare otherwise.

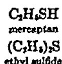
Thioaldehydes and Thioketones. When hydrogen sulfide is passed into a cold mixture of hydrochloric acid with an aldehyde or ketone, the product obtained is a trimeric thioaldehyde or thioketone, which results from rapid polymerization either of monomeric thioaldehyde or thioketone, or of unstable intermediate compounds.

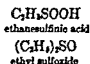


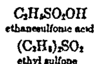
Trithioformaldehyde is of interest because the disulfoxides obtained from it illustrate an unusual type of stereoisomerism (p. 347).

COMPOUNDS OF SULFUR IN HIGHER OXIDATION STATES

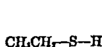
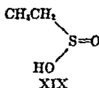
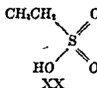
Two series of compounds are known, *viz.*, those from the mercaptans and those from the sulfides:



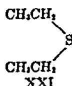
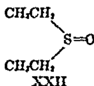
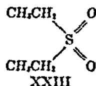




In terms of the classical valence theory, sulfur in the thiol, XVIII, and sulfide, XXI, has a valence of 2, in the sulfinic acid, XIX, and sulfoxide, XXII, a valence of 4, and in the sulfonic acid, XX, and sulfoxide, XXIII, a valence of 6.

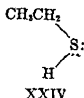




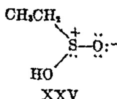
XVIII XIX XX

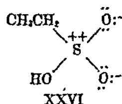




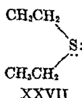
XXI XXII XXIII

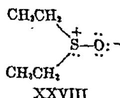
In terms of Lewis structures these formulas become XXIV to XXIX, respectively. In XXIV and XXVII the sulfur is dicovalent, in XXV and XXVIII it is tercovalent, and in XXVI and XXIX it is tetracovalent. The $\overset{+}{S}-\overset{-}{O}$ bonds below are often written as dative bonds, $S \rightarrow O$.

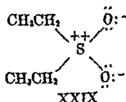






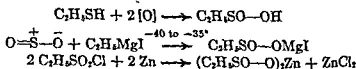






Unless it is assumed that the valence shell of sulfur has ten electrons, it is necessary to write the sulfur-to-oxygen bonds as semipolar double bonds (p. 13). However, the sulfur-to-oxygen distance in methyl sulfone is only 1.44 Å. This is much less than the calculated single bond distance, 1.81 Å, and is even less than the double bond distance, 1.60 Å (Table 2, p. 5). The decided shortening of the bond distance may be due in part to the formal charges associated with the semipolar double bond, in part to double bond character, or to a combination of both. It is possible that resonance involving both types of bonds may be responsible for the abnormal shortening.

Sulfinic Acids. These may be prepared by the controlled oxidation of mercaptans or disulfides, or by the action of sulfur dioxide on Grignard reagents (p. 128) or of zinc dust on sulfonyl chlorides.



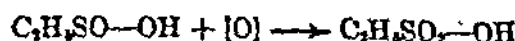
$$C_2H_5SH + 2[O] \longrightarrow C_2H_5SO{-}OH$$
$$O{=}\overset{+}{S}{-}\overset{-}{O} + C_2H_5MgI \xrightarrow{-40 \text{ to } -35^\circ} C_2H_5SO{-}OMgI$$
$$2\,C_2H_5SO_2Cl + 2\,Zn \longrightarrow (C_2H_5SO{-}O)_2Zn + ZnCl_2$$

Either salt can be decomposed by the addition of a strong acid.



$$C_2H_5SO{-}OMgBr + H_3O^+ \longrightarrow \underset{\text{ethanesulfinic acid}}{C_2H_5SO{-}OH} + Mg^{++} + Br^- + H_2O$$

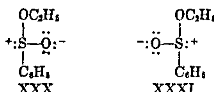
Sulfinic acids are oxidized by concentrated nitric acid or by permanganate to sulfonic acids.



$$C_2H_5SO{-}OH + [O] \longrightarrow C_2H_5SO_2{-}OH$$

The most interesting fact about sulfinic acids is the stereoisomerism shown by some of the derivatives. Thus the ethyl ester of benzenesulfinic acid has been obtained with optical activity. Since the benzene ring is not responsible

for optical activity, the sulfur atom must be. The *dextro-* and *levo-*forms are represented by XXX and XXXI.



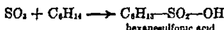
As in sulfonium compounds (p. 340), the sulfur atom cannot be coplanar with the three atoms to which it is attached. Here again the sulfur is essentially an asymmetric sulfur atom. This is due to the unshared electron pair, XXX. Even if the sulfur-to-oxygen bond is a double bond, there still is an unshared electron pair on the sulfur atom, and consequently the sulfur atom is not coplanar with the three atoms to which it is joined.

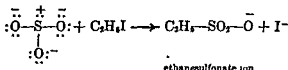
Free sulfinic acids cannot be resolved. This means that the stereoisomers change rapidly into each other. Such a change involves merely the transfer of a proton from one oxygen atom to the other, and thus is a type of tautomerism.

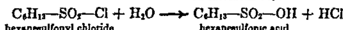
Sulfonic Acids. These are the final oxidation products of mercaptans, disulfides, and sulfinic acids. From these the sulfonic acids are obtained by the action of fuming nitric acid, potassium permanganate, hydrogen peroxide, or other strong oxidizing agent.



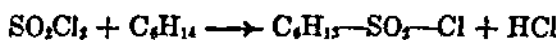
Sulfonic acids may be obtained by sulfonation of alkanes with fuming sulfuric acid (but in low yields, see p. 54), from sulfite ion and alkylating agents (as salts or esters), or by hydrolysis of sulfonyl chlorides.







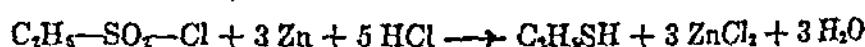
Hydrolysis of sulfonyl chlorides is becoming an important method; for sulfonyl chlorides are produced readily when sulfuryl chloride reacts with alkanes under illumination.



The reaction with bisulfite ion to form a carbon-to-sulfur bond, rather than a carbon-to-oxygen bond may seem unusual until the structure of bisulfite ion is considered. The sulfur atom carries an unshared electron pair, and it is this pair which forms the new bond with the carbon atom of the alkylating reagent rather than one of the nine unshared pairs of the oxygen atoms. The

explanation of this greater reactivity of the sulfur atom may lie in its greater size, for bond formation with the carbon atom could take place with the atoms further apart than if the oxygen atom were forming a bond. Thus the activation energy would be less, and this would permit a much higher reaction rate.

The formation of a mercaptan when a sulfonyl chloride is reduced by zinc and hydrochloric acid shows that there is a carbon-to-sulfur bond in the sulfonyl chloride molecule, and thus in the sulfonic acid molecule.



$$C_2H_5{-}SO_2{-}Cl + 3\,Zn + 5\,HCl \longrightarrow C_2H_5SH + 3\,ZnCl_2 + 3\,H_2O$$

Sulfonic acids are strong acids and are very soluble in water. For purification purposes they are distilled at reduced pressure, because they decompose at atmospheric pressure. Moreover salts with alkali and alkaline earth metals also are quite soluble. An important industrial use depends upon the fact that the calcium salts of sulfonic acids usually are soluble in water. Even the salts of acids having 8 to 16 carbon atoms are water soluble, in contrast to salts of analogous carboxylic acids. These soluble salts are useful surface-active agents, and thus have detergent properties (p. 247). They are replacing soaps for many purposes, more particularly because they are effective in "hard water."

Sulfonic acids, like carboxylic acids, form acid chlorides, esters, amides, etc. The sulfonyl chlorides, like acyl chlorides, are useful reagents for forming esters and amides.

The acids are named by adding sulfonic acid to the name of the hydrocarbon, for example, methanesulfonic acid, and the acid chlorides are named similarly to those of carboxylic acids, for example, methanesulfonyl chloride. A like statement applies to sulfinic acids.

TABLE 67 | **Some Sulfonic Acids and Derivatives**

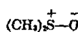
COMPOUND	FORMULA	M.P. °C	B.P. °C	RSO_2Cl B.P. °C	RSO_2NH_2 M.P. °C
Methanesulfonic acid	CH_3SO_3H	+20	167 [a]	161 [b]	90
Ethanesulfonic acid	$C_2H_5SO_3H$	−17		177 [c]	60
Propane-1-sulfonic acid	$n\text{-}C_3H_7SO_3H$	+7.5	136 [d]	77–78 [e]	52
Butane-1-sulfonic acid	$n\text{-}C_4H_9SO_3H$	−15	147 [f]	96–97 [g]	45

[a] At 10 mm. [b] At 730 mm. [c] At 760 mm. [d] At 1 mm. [e] At 13 mm. [f] At 0.5 mm. [g] At 18 mm.

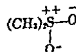
Sulfoxides. These usually can be obtained by oxidation of a sulfide with concentrated nitric acid. With fuming nitric acid they are oxidized to sulfones.



methyl sulfide



methyl sulfoxide



methyl sulfone

Interest in these relatively unimportant compounds centers about the possibility of a type of stereoisomerism which, like that of sulfonium compounds and sulfinic acids, depends upon a nonplanar grouping of atoms about the sulfur atom.

Stereoisomerism of Sulfoxides. *Two isomeric disulfoxides of trithioformaldehyde are known.* If the sulfur atom and its three attached atoms are coplanar, as one would expect on the basis of the older classical valence picture, XXII, page 343, then stereoisomeric forms are not possible, as shown by XXXII, Figure 23. But with a nonplanar grouping about the sulfur atom

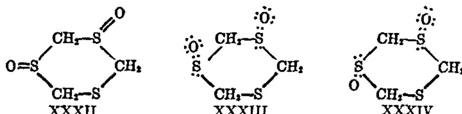


Figure 23 · Trithioformaldehyde Disulfoxide

there are two possibilities, *viz.*, XXXIII, where the two oxygen atoms lie on the same side, and XXXIV, where they lie on opposite sides of the ring. The existence of these isomers is evidence that the sulfur atom in a sulfoxide is not coplanar with the three atoms to which it is attached. This is another example of geometrical, or *cis,trans-* isomerism, for here the ring plays the role of the double bond in isomerism of the maleic-fumaric type by preventing free rotation. The question as to whether the ring is staggered or planar is not pertinent, since it probably is not in a fixed position at ordinary temperatures.

Sulfones. They may be obtained by oxidation of sulfoxides (above) or by reaction of sulfuryl chloride with Grignard reagents.



$$2\ C_2H_5MgBr + SO_2Cl_2 \longrightarrow (C_2H_5)_2SO_2 + MgBr_2 + MgCl_2$$

Sulfones are relatively unimportant. However, many soporifics of the sulfonal type are known and find employment in medicine.

TABLE 68 | **Constants of Some Sulfur Compounds**

RADICAL	MERCAPTAN RSH B.P. °C	RADICALS	SULFIDE R_2S B.P. °C	DISULFIDE R_2S_2 B.P. °C	SULFOXIDE R_2SO B.P. °C	SULFONE R_2SO_2	
						m.p. °C	b.p. °C
Methyl	7.2	Dimethyl	37 3	116–118	8	109	234
Ethyl	37	Diethyl	92.2	153	15	72	246
n-Propyl	*68*	*Di-n-propyl*	*141*	*192*	*18*	29 5	
n-Butyl	98	Di-*n*-butyl	182	101–113 [a]	32	44	

[a] At 15 mm.

PROBLEMS

1. Show three different methods for a practical preparation, from an alcohol, of:

a) *n*-propyl mercaptan
b) *n*-propyl sulfide
c) *n*-butyl mercaptan
d) *n*-butyl sulfide
e) *n*-amyl mercaptan
f) *n*-amyl sulfide
g) *sec*-butyl mercaptan
h) *sec*-butyl sulfide

2. Show two different synthetic methods not involving similar types of reagents for a practical preparation, from an alcohol, of:

a) 1-propanesulfinic acid
b) 1-propanesulfonic acid
c) 1-butanesulfinic acid
d) 1-butanesulfonic acid
e) 1-pentanesulfinic acid
f) 1-pentanesulfonic acid
g) 2-pentanesulfinic acid
h) 2-pentanesulfonic acid

3. Starting with isobutyl alcohol, show the steps involved in a practical laboratory preparation of:

a) isobutyl mercaptan
b) isobutyl sulfide
c) isobutyl sulfoxide
d) isobutyl sulfone
e) 2-methyl-1-propanesulfinic acid
f) 2-methyl-1-propanesulfonic acid
g) sodium isobutyl*dithio*carbonate

4. Indicate the possible stereoisomeric forms of:

a) methylethyl-*n*-butylsulfonium bromide
b) methylethylcarboxymethylsulfonium iodide
c) methylethyl-*sec*-butylsulfonium bromide
d) methylethylallylsulfonium iodide
e) methylethylcrotylsulfonium iodide
f) mercaptal monosulfoxide
g) mercaptal disulfoxide
h) mercaptol monosulfoxide
i) mercaptol disulfoxide
j) methyl 2-propanesulfinate
k) isopropyl ethanesulfinate
l) methyl 2-butanesulfinate
m) *sec*-butyl ethanesulfinate
n) crotyl ethanesulfinate

CHAPTER 21

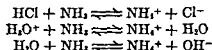
Aliphatic Amines

Amines are organic derivatives of ammonia. In these one, two, or three of the hydrogen atoms of ammonia are replaced by alkyl radicals (or aryl radicals, in the aromatic series).

There are other classes of organic compounds of nitrogen. Of these the most important are: amides, $RCONH_2$, and related compounds (Chap. 22); cyanides, RCN, and isocyanides, RNC (Chap. 23); and nitro compounds, RNO_2 (Chap. 24).

Ammonia. It is well to recall some of the characteristic reactions of ammonia, which amines resemble in so many ways. Like water, ammonia is amphoteric, but since the basic character predominates over the acidic character, the latter often is overlooked. However in some organic derivatives of ammonia the acidic properties predominate over the basic ones.

Ammonia is a base since it accepts a proton from many compounds. Reactions with hydrogen chloride, hydronium ion, and water are all of a type.



$$HCl + NH_3 \rightleftharpoons NH_4^+ + Cl^-$$
$$H_3O^+ + NH_3 \rightleftharpoons NH_4^+ + H_2O$$
$$H_2O + NH_3 \rightleftharpoons NH_4^+ + OH^-$$

The first represents neutralization of ammonia by hydrogen chloride, gaseous or liquid; the second, neutralization by an acid in aqueous solution; and the third, the formation of hydroxide ion in aqueous solution. They are all equilibrium reactions, but the first and second proceed much further towards completion than the third. This is because water is a much weaker acid than hydrogen chloride or hydronium ion, and thus does not part with a proton as easily. Conversely, hydroxide ion is more strongly basic than either a chloride ion or a water molecule, and thus, by competing more strongly for a proton of ammonium ion, promotes the reverse reaction. Ammonium ion is thus an acid. In terms of the Brönsted concept of acids and bases, it is called the conjugate acid of ammonia. This means that it is formed from ammonia by addition of a proton. Similarly, hydronium ion is the conjugate acid of water.

The base constant of ammonia in aqueous solution, neglecting activities, is given as K,

$$K = \frac{[NH_4^+][OH^-]}{[NH_3][H_2O]} \qquad K_b = K[H_2O] = \frac{[NH_4^+][OH^-]}{[NH_3]}$$

which becomes K_b on elimination of the H_2O term, which is assumed to be constant. Actually part of the ammonia in aqueous solution is hydrated to ammonium hydroxide, and this usually is regarded as the source of hydroxide ion.

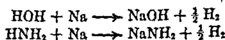


$$NH_3 + H_2O \rightleftharpoons NH_4OH \rightleftharpoons NH_4^+ + OH^-$$

If all of the ammonia were hydrated, then the K_b of ammonia would be the K_b of ammonium hydroxide. But since only a part is hydrated, the true dissociation constant of ammonium hydroxide is higher than the K_b of ammonia, sometimes called the apparent dissociation constant of ammonium hydroxide.

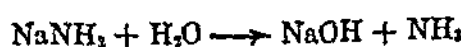
Structurally ammonium hydroxide exists by virtue of hydrogen bonding. A proton of the water molecule is attracted by the unshared electron pair of the nitrogen atom of an ammonia molecule, thus: $H_3N—H—O—H$.

Ammonia has acid properties, as shown by the formation of sodamide with metallic sodium. This reaction is similar to the action of metallic sodium on water.



$$HOH + Na \longrightarrow NaOH + \tfrac{1}{2} H_2$$
$$HNH_2 + Na \longrightarrow NaNH_2 + \tfrac{1}{2} H_2$$

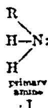
Sodium reacts with liquid ammonia, or with gaseous ammonia at elevated temperatures, 300 to 400°. Sodamide is completely hydrolyzed when added to water.



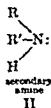
$$NaNH_2 + H_2O \longrightarrow NaOH + NH_3$$

This shows that water is a much stronger acid than ammonia, for it is a general principal that a stronger acid liberates a weaker acid from an ionic salt of the latter. It is assumed here that sodamide is an ionic, not a covalent compound. Thus the basic properties of ammonia are stronger than those of water, while the acidic properties are weaker. As a base in aqueous solution, ammonia has a K_b value of 1.8×10^{-5}. A value for K_a has been reported, *viz.*, 1.9×10^{-33}, but is to be regarded as approximate only.

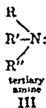
Classification of Amines. There are three classes of amines, *viz.*, primary, I, secondary, II, and tertiary, III, depending upon the number of hydrogen atoms of ammonia replaced by alkyl groups. In addition to these there is a fourth type of base which is derived from ammonium hydroxide. This is a quaternary ammonium base, IV. R, R′, and R″ may be alike or dissimilar.



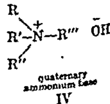
primary amine
I



secondary amine
II



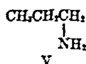
tertiary amine
III

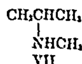
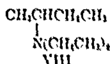


quaternary ammonium base
IV

The words, primary, secondary, and tertiary have not the same meaning with amines that they have with alcohols. With amines they signify the number of alkyl groups attached to the nitrogen atom, whereas in alcohols they signify the number of alkyl groups attached to the carbon atom to which the hydroxyl group is attached (p. 137).

Nomenclature of Amines. In the I.U.C. system primary amines are aminoalkanes (NH_2 = amino), secondary amines are alkylaminoalkanes, and tertiary are dialkylaminoalkanes. Usually, however, they are named as alkylamines (alkylammonias). Thus V is 1-aminopropane or n-propylamine, VI is 2-aminopropane or isopropylamine, VII is 2-methylaminopropane or methylisopropylamine, and VIII is 2-diethylaminobutane or diethyl-sec-butylamine.

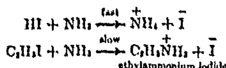


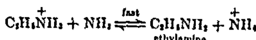
V and VI are primary, VII is secondary, and VIII is tertiary.

Preparation of Amines. *Primary amines.* In most of the cases below, formation of secondary and to some extent of tertiary amines is observed. This is because the primary amine reacts either with the reagent, as in (1), or with an intermediate, as in (6). Formation of secondary or tertiary amines usually is not observed in (3) and (7).

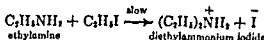
1. *From ammonia and alkyl halides.* When an alcoholic solution of ammonia is heated in a sealed tube with an alkyl iodide, methylammonium iodide is slowly formed in an addition reaction which, formally, resembles the addition of hydriodic acid to ammonia.



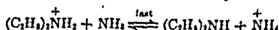
In the presence of unreacted ammonia there is competition for the proton of the ethylammonium ion, the position of equilibrium depending upon the relative strengths and concentrations of the two bases.



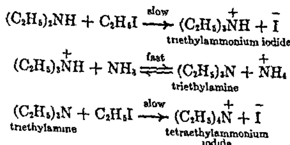
Ethylamine, like ammonia, reacts with ethyl iodide. Diethylammonium iodide is formed. This reaction becomes more important as the concentration of ethylamine increases.



This reacts with other bases present, to form diethylamine.



The addition reaction can continue with formation of other products.



The final product may be a mixture of the different amines and their salts. If the primary amine is the desired product, a large excess of ammonia should be taken. In case one of the salts has a low solubility in the solution and crystallizes out, it can become the main product.

In order to liberate an amine from its salt, a strong base is added.



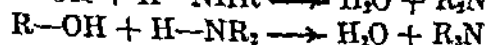
By fractional distillation a separation can be made of the primary, secondary, and tertiary amines from one another, except however, this is a laborious procedure in the case of the methyl compounds (Table 70, p. 356).

2. *From ammonia and alcohols.* When the vapor of an alcohol is passed with ammonia over certain catalytic substances at temperatures around 300°, water is eliminated and amines are formed.

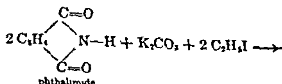


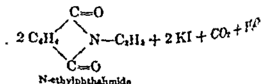
Good catalysts for this reaction are the usual dehydrating catalysts, especially aluminum and tungsten oxides. Unfortunately, secondary and tertiary amines also are formed, consequently the operation does not yield pure products.



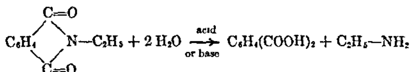


3. *From an imide and alkyl halide.* Succinimide can be used, but phthalimide is the usual reagent. It is converted into the potassium salt by potassium ethoxide in alcohol. The solid is heated with an alkyl iodide; or, more simply, phthalimide, the alkyl halide, and dry potassium carbonate are heated together.

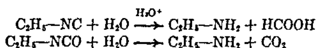




On hydrolysis, N-ethylphthalimide is converted to phthalic acid and ethylamine. This method has the advantage that the primary amine is uncontaminated by any secondary or tertiary amine.

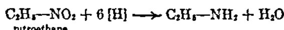


4. *From isocyanides and isocyanates, by hydrolysis.* Isocyanides, R—NC, undergo acid hydrolysis, and isocyanates, R—NCO, undergo acid or base hydrolysis to yield primary amines (p. 395).



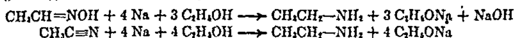
Aside from the historical interest of the last reaction, by which Wurtz in 1848 obtained the first amine, ethylamine, the reactions are not important from a preparative standpoint.

5. *From nitroparaffins, by reduction.* The nitro group is easily reduced to the amino group (p. 404).



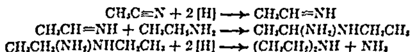
This is becoming an important method of preparation, since nitroparaffins are now available. A side reaction leads to the formation of the secondary amine. When the reducing agent is hydrogen, this can be minimized by carrying on the reaction in the presence of acetic anhydride, which acetylates the amine as it is formed. This prevents reactions which lead to the formation of the secondary and tertiary amine.

6. *From other compounds, by reduction.* Compounds in which carbon is attached to nitrogen by a multiple bond are reduced to primary amines. These include oximes, RCH=NOH (p. 270), hydrazones, $RCH{=}NNH_2$ (p. 271), and nitriles, RCN (p. 391).



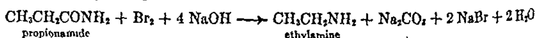
Reduction of oximes and hydrazones allows amines to be prepared from aldehydes or ketones.

Nitrile reduction is important for higher members, since nitriles can be obtained from higher fatty acids. Formation of the secondary amine is believed to arise from reaction of the primary amine with the imine, the first reduction product of the nitrile.



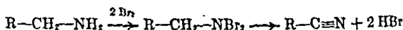
7. *From amides, by the Hofmann degradation.* When an amide, $RCONH_2$, is heated with an alkaline hypochlorite or hypobromite, it undergoes a com-

plicated series of reactions (see p. 374), with loss of carbon dioxide and formation of a primary amine of one less carbon atom.



$$\underset{\text{propionamide}}{CH_3CH_2CONH_2} + Br_2 + 4\,NaOH \longrightarrow \underset{\text{ethylamine}}{CH_3CH_2NH_2} + Na_2CO_3 + 2\,NaBr + 2\,H_2O$$

This is a generally useful method for preparing primary amines free of secondary and tertiary amines, and gives satisfactory yields for lower amines up to n-heptylamine (70%). Higher amines are obtained in poor yield, because of nitrile formation.

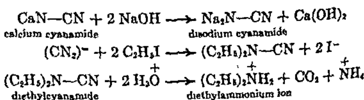


$$R{-}CH_2{-}NH_2 \xrightarrow{2\,Br_2} R{-}CH_2{-}NBr_2 \longrightarrow R{-}C{\equiv}N + 2\,HBr$$

Another degradation method similar to this is the Curtius method, from acid azides (p. 375).

Secondary amines. These can be prepared by alkylation of primary amines but are contaminated with tertiary amines. It is possible to prepare in this way a secondary amine with two different alkyl radicals. Other methods are available for pure secondary amines.

8. *From sodium cyanamide.* Calcium cyanamide (p. 397) is converted first to the sodium salt by sodium hydroxide, this with an alkyl halide gives a dialkyl derivative, and this undergoes hydrolysis when heated with aqueous acid or base.

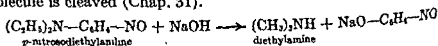


$$\underset{\text{calcium cyanamide}}{CaN{-}CN} + 2\,NaOH \longrightarrow \underset{\text{disodium cyanamide}}{Na_2N{-}CN} + Ca(OH)_2$$

$$(CN_2)^{=} + 2\,C_2H_5I \longrightarrow (C_2H_5)_2N{-}CN + 2\,I^-$$

$$\underset{\text{diethylcyanamide}}{(C_2H_5)_2N{-}CN} + 2\,H_3\overset{+}{O} \longrightarrow \underset{\text{diethylammonium ion}}{(C_2H_5)_2\overset{+}{N}H_2} + CO_2 + \overset{+}{N}H_4$$

9. *From para-nitrosodialkylanilines.* When heated with aqueous alkalies the molecule is cleaved (Chap. 31).



$$\underset{p\text{-nitrosodiethylaniline}}{(C_2H_5)_2N{-}C_6H_4{-}NO} + NaOH \longrightarrow \underset{\text{diethylamine}}{(CH_3)_2NH} + NaO{-}C_6H_4{-}NO$$

TABLE 69 | **Constants of Some Normal Primary Amines**

NAME	FORMULA	M.P. °C	B.P. °C	SOLY. IN H_2O cc./100 cc.	SOLY. IN H_2O g./100 g.	$K_b \times 10^4$	DIEL. CONST. 25°
Methylamine	CH_3NH_2	−92	−7.5	51,100 [a]		4.4	9
Ethylamine	$C_2H_5NH_2$	−80	16.6	32,100 [a]	misc.	4.7	6 [b]
n-Propylamine	$C_3H_7NH_2$	−83	48.7		misc.	3.8	5 [c]
n-Butylamine	$C_4H_9NH_2$	−50	78		v. sol. [d]	4.1	5 [e]
n-Amylamine	$C_5H_{11}NH_2$	−55	104		sol.	4.4	4 [f]
n-Hexylamine	$C_6H_{13}NH_2$	−19	130		s sol.		

[a] At 60°. [b] 6.94 at 10°. [c] 5.5 for isopropylamine at 20°. [d] Miscible when heated. [e] 5.3 at 21°. [f] 4.5 at 22°.

The solubility of lower amines in water is high. Solubility of higher amines becomes progressively less. The basic strengths, K_b, of the three classes do not differ markedly from that of ammonia, but vary somewhat, the order usually being: secondary > primary > tertiary.

Reactions of Amines. Many of these are related to the chemistry of ammonia. This is especially true of reactions with acids, acylating agents, alkylating agents, nitrous acid, halogens, and Grignard reagents. The nitrogen-to-carbon bond in general is not cleaved (exceptions, reaction with nitrous acid and pyrolysis of salts), in this respect being more stable than the oxygen-to-carbon bond of alcohols. It is significant that the bond dipole moments are 0.4 D and 0.8 D, respectively (Table 15, p. 33).

1. *Basic properties.* The most outstanding general characteristic property of the amines is the ability to form salts with strong acids They are the **organic bases.** The reaction may be carried out by mixing suitable solutions of the acid and base as, for example, aqueous solutions or alcoholic solutions, or by passing the anhydrous hydrogen halide into a solution of the amine in some suitable solvent.



$$C_2H_5{-}NH_2 + H{-}X \longrightarrow C_2H_5{-}\overset{+}{N}H_3 + X^-$$

Salt formation in the case of ethylamine, like that of ammonia, takes place by the transfer of a proton, with the formation of positive ethylammonium ion and negative halide ion. The ionic nature of the compound is indicated by the fact that its aqueous solution is electrically conducting and gives an immediate precipitate of silver halide on the addition of silver ion. Diethylamine and triethylamine likewise form salts with strong acids in an analogous fashion.

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$CH_3CH_2NH_3Cl$
ethylammonium chloride

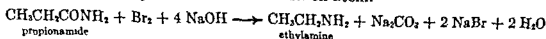


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ethylamine hydrochloride

Double salts are formed with platinum chloride, such as ethylammonium chloroplatinate, $(C_2H_5NH_3)_2PtCl_6$. In general these are easily crystallizable solids, sparingly soluble in alcohol, and often are used for purposes of purification.

Addition of strong base liberates an amine from its salt. The amine, if of low molecular weight and therefore soluble in water (Tables 69 and 70), may

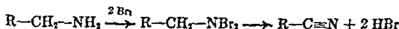
plicated series of reactions (see p. 374), with loss of carbon dioxide and formation of a primary amine of one less carbon atom.



$$CH_3CH_2CONH_2 + Br_2 + 4\,NaOH \longrightarrow CH_3CH_2NH_2 + Na_2CO_3 + 2\,NaBr + 2\,H_2O$$

propionamide → ethylamine

This is a generally useful method for preparing primary amines free of secondary and tertiary amines, and gives satisfactory yields for lower amines up to *n*-heptylamine (70%). Higher amines are obtained in poor yield, because of nitrile formation.

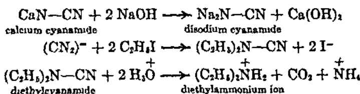


$$R{-}CH_2{-}NH_2 \xrightarrow{2\,Br_2} R{-}CH_2{-}NBr_2 \longrightarrow R{-}C{\equiv}N + 2\,HBr$$

Another degradation method similar to this is the Curtius method, from acid azides (p. 375).

Secondary amines. These can be prepared by alkylation of primary amines but are contaminated with tertiary amines. It is possible to prepare in this way a secondary amine with two different alkyl radicals. Other methods are available for pure secondary amines.

8. *From sodium cyanamide.* Calcium cyanamide (p. 397) is converted first to the sodium salt by sodium hydroxide, this with an alkyl halide gives a dialkyl derivative, and this undergoes hydrolysis when heated with aqueous acid or base.



$$CaN{-}CN + 2\,NaOH \longrightarrow Na_2N{-}CN + Ca(OH)_2$$

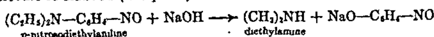
calcium cyanamide → disodium cyanamide

$$(CN_2)^{=} + 2\,C_2H_5I \longrightarrow (C_2H_5)_2N{-}CN + 2\,I^-$$

$$(C_2H_5)_2N{-}CN + 2\,H_3\overset{+}{O} \longrightarrow (C_2H_5)_2\overset{+}{N}H_2 + CO_2 + \overset{+}{N}H_4$$

diethylcyanamide → diethylammonium ion

9. *From para-nitrosodialkylanilines.* When heated with aqueous alkalies the molecule is cleaved (Chap. 31).



$$(C_2H_5)_2N{-}C_6H_4{-}NO + NaOH \longrightarrow (CH_3)_2NH + NaO{-}C_6H_4{-}NO$$

p-nitrosodiethylaniline → diethylamine

TABLE 69 | **Constants of Some Normal Primary Amines**

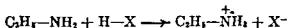
NAME	FORMULA	M.P. °C	B.P. °C	SOLY. IN H_2O cc./100 cc.	SOLY. IN H_2O g/100 g.	$K_b \times 10^4$	DIEL. CONST. 25°
Methylamine	CH_3NH_2	−92	−7.5	51,100 [a]		4.4	9.4
Ethylamine	$C_2H_5NH_2$	−80	16.6	32,100 [a]	misc.	4.7	6 [b]
n-Propylamine	$C_3H_7NH_2$	−83	48.7		misc. [c]	3.8	5 [c]
n-Butylamine	$C_4H_9NH_2$	−50	78		v. sol. [d]	4.1	5 [e]
n-Amylamine	$C_5H_{11}NH_2$	−55	104		sol.	4.4	4 [f]
n-Hexylamine	$C_6H_{13}NH_2$	−19	130		s. sol.		

[a] At 60°. [b] 6.94 at 10°. [c] 5.5 for isopropylamine at 20°. [d] Miscible when heated. [e] 5.3 at 21°. [f] 4.5 at 22°.

The solubility of lower amines in water is high. Solubility of higher amines becomes progressively less. The basic strengths, K_b, of the three classes do not differ markedly from that of ammonia, but vary somewhat, the order usually being: secondary > primary > tertiary.

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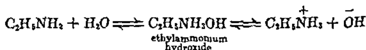
be driven from the solution by heating, or in some cases it may be extracted with ether or other suitable solvent. If of high molecular weight, it will separate as a second liquid phase. Thus an amine salt may be purified by crystallization and the amine recovered in a pure form.

TABLE 70 | **Some Primary, Secondary, and Tertiary Amines**

NAME	FORMULA	M.P. °C	B.P. °C	SOLY. IN H_2O G./100 G.	$K_b \times 10^4$	DIEL. CONST. 25°
Methylamine	CH_3NH_2	−92	−7.5	v. sol.	4.4	9.4
Dimethylamine	$(CH_3)_2NH$	−96	7.5	v. sol.	5.1	5.3
Trimethylamine	$(CH_3)_3N$	−117.2	3.2	91	0.6	2.4
Ethylamine	$C_2H_5NH_2$	−80	16.6	misc.	4.7	6[a]
Diethylamine	$(C_2H_5)_2NH$	−39	55	v. sol	9.5	3.4[b]
Triethylamine	$(C_2H_5)_3N$	−114.7	89.4	14.2	5.5	2.42
n-Propylamine	$C_3H_7NH_2$	−83	49	misc.	3.8	5[c]
Di-*n*-propylamine	$(C_3H_7)_2NH$	−63	110	s. sol.	8.1	2.5[d]
Tri-*n*-propylamine	$(C_3H_7)_3N$		156.5	s. sol.	4.5	
Tetramethylammonium hydroxide	$(CH_3)_4NOH$		dec. 135	220	large	

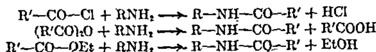
[a] 6.94 at 10°. [b] 3.6 at 22°. [c] 5.5 for isopropylamine at 20°. [d] 2.9 at 21°.

In aqueous solution there is an equilibrium between the amine and the hydrated form, which may be and often is regarded as the source of hydroxide ion.



$$C_2H_5NH_2 + H_2O \rightleftharpoons \underset{\text{ethylammonium hydroxide}}{C_2H_5NH_3OH} \rightleftharpoons C_2H_5\overset{+}{N}H_3 + \overset{-}{O}H$$

2. *Acylation of amines.* Primary and secondary amines, like ammonia, react rapidly and exothermically with acid chlorides, less vigorously with anhydrides, and slowly with esters to form N-alkylated amides. Tertiary amines do not form acyl derivatives.



$$R'\text{—CO—Cl} + RNH_2 \longrightarrow R\text{—NH—CO—}R' + HCl$$
$$(R'CO)_2O + RNH_2 \longrightarrow R\text{—NH—CO—}R' + R'COOH$$
$$R'\text{—CO—OEt} + RNH_2 \longrightarrow R\text{—NH—CO—}R' + EtOH$$

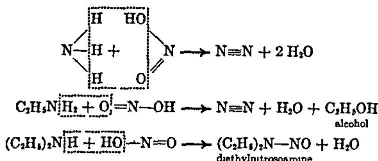
Anhydrides are especially useful for converting primary and secondary amines to acyl derivatives, either for preparative purposes or for distinguishing from tertiary amines. Acyl halides react rapidly with tertiary amines, often with considerable evolution of heat, to yield addition compounds, actually quaternary salts, $R_3\overset{+}{N}COR + Cl^-$, many of which are solid. This type of complex, when added to water is decomposed; the acyl halide undergoes hydrolysis, and the tertiary amine is converted to the hydrohalide. Acyl halides often react with only about half of a primary or secondary amine. This is because the hydrohalic acid formed converts unreacted amine to the hydrohalic salt, and this reacts only very slowly with the acyl halide.

For distinguishing primary and secondary amines from tertiary amines, acyl halides are especially useful. The reaction mixture is added to water, which hydrolyzes unchanged acyl halide. Any unchanged amine is converted to a salt, usually soluble. Amides are neutral substances. The amides of primary and secondary amines often are solid, and only slightly soluble in water. However, lower amides often are liquids, and somewhat soluble in water. On this account benzoyl chloride, C_6H_5COCl, is preferred. Also benzenesulfonyl chloride, $C_6H_5SO_2Cl$, is especially useful with dilute aqueous alkali (see Hinsberg test, p. 458).

Tertiary amines are valuable catalysts in the acylation of alcohols and other hydroxy compounds, for example, phenols, glycols, and hydroxy acids, by means of acyl halides or anhydrides. The addition compound first formed is itself very reactive. Acylations can be accomplished at lower temperatures, and normal products are obtained. Tertiary alcohols give the expected ester under these conditions (see p. 220).

3. *Reaction with nitrous acid.* The reaction is carried out in cold aqueous solution with sodium nitrite and hydrochloric acid, since nitrous acid is known only in dilute aqueous solution and is unstable. Primary, secondary, and tertiary amines undergo characteristically different reactions, which serve for distinguishing them

It is instructive to refer the reactions to the more fundamental one of ammonia with nitrous acid, in which two molecules of water are eliminated, and nitrogen is formed. Thus with a primary or secondary amine one molecule of water is formed, but a tertiary amine does not react, since it lacks the N—H bond.

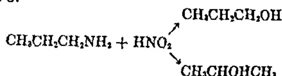


A primary amine yields nitrogen gas and an alcohol, a secondary amine yields a nitrosoamine, no nitrogen being evolved, and a tertiary amine does not react, except that sometimes a slightly soluble nitrite salt may form. However, oxides of nitrogen may be evolved, owing to the instability of nitrous acid, so that gas evolution may take place in any event. This is decreased by keeping the solution cold.

Sometimes a nitrous ester is formed, because of a rapid reaction of nitrous acid with the alcohol (p. 231). This is especially true with methylamine. Methyl nitrite, a gas, passes out with the nitrogen.

The reaction with nitrous acid makes possible the conversion of primary amines to alcohols. But when the reaction is carried out with *n*-propyl-

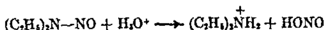
amine, a mixture of n-propyl and isopropyl alcohol results in the approximate ratio of 2 to 3.



$$CH_3CH_2CH_2NH_2 + HNO_2 \rightarrow CH_3CH_2CH_2OH \text{ and } CH_3CHOHCH_3$$

One would not predict the formation of isopropyl alcohol, for it is not the product of the normal reaction. Abnormal reaction products are common in reactions between amines and nitrous acid. However, the abnormal reaction becomes progressively less important with increase in the number of carbon atoms. No secondary alcohol is obtained from *n*-nonylamine.

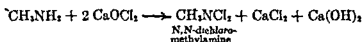
Nitrosoamines, from secondary amines, are neutral substances and do not form salts with acids. The lower members are volatile, colorless liquids soluble in water, and the higher ones are insoluble in water. When heated with hydrochloric acid, a nitrosoamine is hydrolyzed to the amine and nitrous acid.



$$(C_2H_5)_2N{-}NO + H_3O^+ \longrightarrow (C_2H_5)_2\overset{+}{N}H_2 + HONO$$

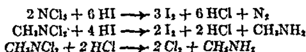
Separation of a secondary from a tertiary amine can be effected through the formation of the nitrosoamine, and the secondary amine can be regenerated.

4. *Reaction with halogens.* Chlorine, bromine, or iodine under basic conditions replaces one or both hydrogen atoms attached to nitrogen.



$$CH_3NH_2 + 2\,CaOCl_2 \longrightarrow \underset{\text{N,N-dichloromethylamine}}{CH_3NCl_2} + CaCl_2 + Ca(OH)_2$$

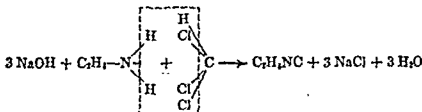
Halogen attached to nitrogen, like the chlorine in nitrogen trichloride, is oxidizing and liberates iodine from hydriodic acid, and even chlorine from hydrochloric acid.



$$2\,NCl_3 + 6\,HI \longrightarrow 3\,I_2 + 6\,HCl + N_2$$
$$CH_3NCl_2 + 4\,HI \longrightarrow 2\,I_2 + 2\,HCl + CH_3NH_2$$
$$CH_3NCl_2 + 2\,HCl \longrightarrow 2\,Cl_2 + CH_3NH_2$$

The presence of the organic radical adds stability. Thus N,N-dichloromethylamine distils at 59 to 60° with some decomposition, whereas nitrogen trichloride is unstable and sometimes decomposes with explosive violence under shock.

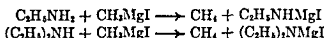
5. *Reaction with chloroform; the carbylamine reaction.* In the presence of alkali, primary amines form isocyanides with chloroform, while secondary and tertiary amines do not react.



$$3\,NaOH + C_2H_5{-}NH_2 + HCCl_3 \longrightarrow C_2H_5NC + 3\,NaCl + 3\,H_2O$$

Isocyanides have powerful, characteristically disagreeable odors. The reaction often is used as a test for a primary amine. Only a very small amount should be taken for the test, because it is so delicate that a secondary or tertiary amine, if contaminated with a small amount of primary amine, will also give a positive test.

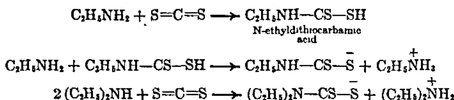
6. *Reaction with Grignard reagents.* A primary or secondary amine reacts with methylmagnesium iodide in the Zerewitinoff test (p. 127), and a tertiary amine does not.



$$C_2H_5NH_2 + CH_3MgI \longrightarrow CH_4 + C_2H_5NHMgI$$
$$(C_2H_5)_2NH + CH_3MgI \longrightarrow CH_4 + (C_2H_5)_2NMgI$$

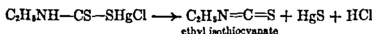
Thus a primary or secondary amine resembles ammonia in possessing labile hydrogen. Other Grignard reagents react similarly. Tertiary amines form complexes with Grignard reagents and actually have been used as solvents for the Grignard reaction, replacing ether.

7. *Reaction with carbon bisulfide.* A primary or secondary amine, but not a tertiary amine, reacts with carbon bisulfide in alcoholic solution to form an alkyldithiocarbamic acid. This at once reacts with a second molecule of the base to form a salt.



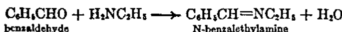
$$C_2H_5NH_2 + S{=}C{=}S \longrightarrow \underset{\text{N-ethyldithiocarbamic acid}}{C_2H_5NH{-}CS{-}SH}$$
$$C_2H_5NH_2 + C_2H_5NH{-}CS{-}SH \longrightarrow C_2H_5NH{-}CS{-}\overset{-}{S} + C_2H_5\overset{+}{N}H_3$$
$$2\,(C_2H_5)_2NH + S{=}C{=}S \longrightarrow (C_2H_5)_2N{-}CS{-}\overset{-}{S} + (C_2H_5)_2\overset{+}{N}H_2$$

An isothiocyanate (mustard oil) is formed by heating some heavy metal salts of the monoalkyl derivatives, for example, the mercury salts.



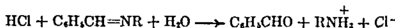
$$C_2H_5NH{-}CS{-}SHgCl \longrightarrow \underset{\text{ethyl isothiocyanate}}{C_2H_5N{=}C{=}S} + HgS + HCl$$

8. *Reaction with benzaldehyde.* A primary amine reacts with benzaldehyde.



$$\underset{\text{benzaldehyde}}{C_6H_5CHO} + H_2NC_2H_5 \longrightarrow \underset{\text{N-benzalethylamine}}{C_6H_5CH{=}NC_2H_5} + H_2O$$

Compounds of this type are insoluble in water and in cold dilute acids. They readily undergo acid hydrolysis, which is essentially a reversal of the reaction.

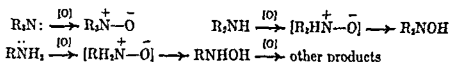


$$HCl + C_6H_5CH{=}NR + H_2O \longrightarrow C_6H_5CHO + R\overset{+}{N}H_3 + Cl^-$$

It is characteristic of the double bond between carbon and nitrogen that it is easily hydrolyzed under acid conditions, to yield an aldehyde or ketone, as in the case of oximes and hydrazones (p. 271).

9. *Reaction with oxidizing agents.* Different oxidizing agents produce different results. Hydrogen peroxide, persulfuric acid, peracetic acid, and similar reagents first form amine oxides. Amine oxides of tertiary amines are stable (p. 362), but those of secondary and primary are unstable. They re-

arrange to hydroxylamine derivatives and, in the case of the primary, further oxidation takes place.

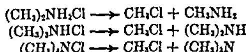


Potassium permanganate under alkaline conditions easily attacks all amines; in acid solution the reaction is much slower. From a primary amine, ammonia, aldehyde, acid, and other products may result. Oxidation is believed to involve formation of an imine, RCH=NH, which readily hydrolyzes to an aldehyde.



Amines burn in oxygen or in air with formation of carbon dioxide, water vapor, nitrogen, and sometimes a little oxide of nitrogen. It will be recalled that ammonia undergoes flame combustion only with difficulty.

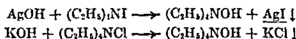
10. *Heating alkylammonium chlorides.* At distillation temperatures a molecule of alkyl chloride is eliminated from the hydrochloride of a secondary or tertiary amine, or from a quaternary ammonium chloride.



This is the reverse of the preparation reaction (p. 351). When different groups are present, usually the smallest is eliminated. The methyl group is eliminated the most easily of alkyl groups.

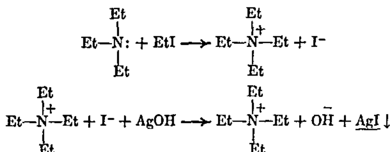
Quaternary Ammonium Bases. Tetraethylammonium iodide (trimethylamine ethiodide) is the final product from the reaction of ethyl iodide with ammonia (p. 352) It is prepared more conveniently from triethylamine and ethyl iodide, which react readily when heated. In general, tertiary amines react readily with alkyl iodides or alkyl sulfates to form quaternary ammonium salts. These possess typical salt characteristics in being solid and readily soluble in water, and they impart conductivity to aqueous solutions.

When excess of silver oxide is added to the aqueous solution of tetraethylammonium iodide, silver iodide is precipitated. Evaporation of the aqueous solution at reduced pressure yields a white crystalline solid, tetraethylammonium hydroxide, very soluble in water. It is a strong base, and its aqueous solution readily absorbs carbon dioxide from the air. When heated, it undergoes decomposition. It is a typical quaternary ammonium base. The base may be obtained also in alcoholic solution from the chloride and potassium hydroxide, as a result of the slight solubility of potassium chloride.



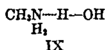
The strongly basic character of tetraethylammonium hydroxide, like that of quaternary ammonium bases in general, is due to the fact that it is com-

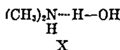
pletely ionized in aqueous solution into positive tetraethylammonium ions and negative hydroxide ions. Even in the solid state it is composed of ions, for there cannot be a covalent bond between nitrogen and oxygen, since this would violate the octet rule. The quaternary iodide also is composed of ions. The formation of the quaternary salt involves the attachment of the fourth ethyl radical as a positive ion, and the formation of the base involves replacing iodide ion by hydroxide ion.

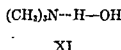


There is no way for a covalent bond to be formed from nitrogen to either oxygen or iodine, even though the iodine atom does expand its octet sometimes.

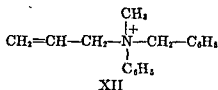
In contrast to the quaternary bases, primary, secondary, and tertiary amines are much weaker bases. The hydroxides which they form in water are only partially ionized. They have structures similar to that of ammonium hydroxide (p. 350). The hydroxides from primary, secondary, and tertiary amines are believed to have the structures IX, X, and XI respectively.

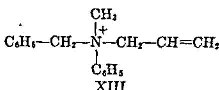






Stereochemistry of Quaternary Ammonium Salts. A number of quaternary ammonium salts have been resolved into *dextro-* and *levo-*forms. In such cases usually there are four different radicals attached to the nitrogen atom. These groups are arranged tetrahedrally about the nitrogen atom. Thus the explanation of optical isomerism of quaternary ammonium compounds is like that of carbon compounds and the nitrogen atom is an asymmetric nitrogen atom. Many quaternary ammonium salts racemize easily. Usually an allyl or a benzyl radical should be present. The first compound to be obtained in optically active forms was methyl-allyl-phenyl-benzylammonium iodide (1899). The two forms of the ions are shown as XII and XIII.





Proof that the four carbon atoms about a tetracovalent nitrogen atom are arranged at tetrahedral corners has been obtained from the crystal structure

arrange to hydroxylamine derivatives and, in the case of the primary, further oxidation takes place.

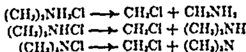


Potassium permanganate under alkaline conditions easily attacks all amines; in acid solution the reaction is much slower. From a primary amine, ammonia, aldehyde, acid, and other products may result. Oxidation is believed to involve formation of an imine, RCH=NH, which readily hydrolyzes to an aldehyde.



Amines burn in oxygen or in air with formation of carbon dioxide, water vapor, nitrogen, and sometimes a little oxide of nitrogen. It will be recalled that ammonia undergoes flame combustion only with difficulty.

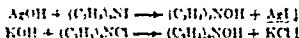
10. *Heating alkylammonium chlorides.* At distillation temperatures a molecule of alkyl chloride is eliminated from the hydrochloride of a secondary or tertiary amine, or from a quaternary ammonium chloride.



This is the reverse of the preparation reaction (p. 351). When different groups are present, usually the smallest is eliminated. The methyl group is eliminated the most easily of alkyl groups.

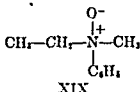
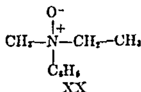
Quaternary Ammonium Bases. Tetraethylammonium iodide (triethylamine ethiodide) is the final product from the reaction of ethyl iodide with ammonia (p. 352) It is prepared more conveniently from triethylamine and ethyl iodide, which react readily when heated. In general, tertiary amines react readily with alkyl iodides or alkyl sulfates to form quaternary ammonium salts. These possess typical salt characteristics in being solid and readily soluble in water, and they impart conductivity to aqueous solutions.

When excess of silver oxide is added to the aqueous solution of tetraethylammonium iodide, silver iodide is precipitated. Evaporation of the aqueous solution at reduced pressure yields a white crystalline solid, tetraethylammonium hydroxide, very soluble in water. It is a strong base, and its aqueous solution readily absorbs carbon dioxide from the air. When heated, it undergoes decomposition. It is a typical quaternary ammonium base. The base may be obtained also in alcoholic solution from the chloride and potassium hydroxide, as a result of the slight solubility of potassium chloride.

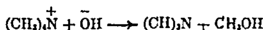


The strongly basic character of tetraethylammonium hydroxide, like that of quaternary ammonium bases in general, is due to the fact that it is com

Optical isomerism has been observed with amine oxides, for just as in the case of quaternary ammonium salts, the four attached atoms are arranged at tetrahedral corners. The active forms of methylethylphenylamine oxide, XIX and XX, represent the first example of this kind of optical isomerism (1908).

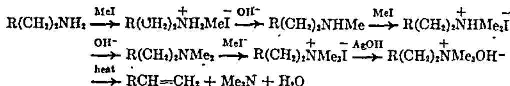
Pyrolysis of Quaternary Ammonium Bases. Tetramethylammonium hydroxide when heated decomposes to trimethylamine and methanol.



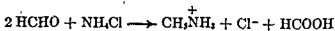
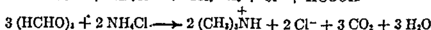
Other quaternary bases usually decompose differently. When a radical is present with a hydrogen atom on the β-carbon atom, the hydrogen atom forms a molecule of water with the hydroxyl group, with production of an olefin and trimethylamine.



This is a general method for degradation of amino compounds, and has been valuable in structural determination of naturally occurring bases, especially of alkaloids (Chap. 45). Any primary amine, RCH_2NH_2, can be converted into the quaternary ammonium base by **exhaustive methylation**, *i.e.*, by alternate reactions with methyl iodide and base to the quaternary ammonium iodide, then with silver oxide; or more simply with a mixture of methyl iodide and silver oxide. In this case the silver oxide converts the first addition compound at once to the free methylated amine (p. 351), which then undergoes further methylation.



Methylamine and Trimethylamine. These are prepared in unique reactions, the first by heating aqueous formaldehyde (formalin) and ammonium chloride, the second by heating dry paraformaldehyde and ammonium chloride.

The first is essentially a dismutation reaction, for one mole of formaldehyde is oxidized to formic acid, and another is reduced to the stage of methanol. Some dimethylamine salt is formed also. The second reaction also involves oxidation and reduction.

of tetramethylammonium iodide and tetraethylammonium iodide, as determined by means of X-ray analysis (1928). Also, the determination of the structure of urotropin by X-ray methods showed that the three carbon-to-nitrogen bonds at each nitrogen atom make tetrahedral angles with each other (p. 280).

Stereoisomeric forms of tercovalent nitrogen do not exist. This result would not be expected, since the nitrogen atom is not coplanar with the three atoms to which it is joined. The arrangement is similar to that in sulfonium ions (p. 310). However, numerous attempts to resolve tertiary amines of the type RR'R''N have resulted in failure. It is believed that one of the modes of vibration of the ammonia molecule involves a very rapid passage of the nitrogen atom through the plane of the other three atoms.

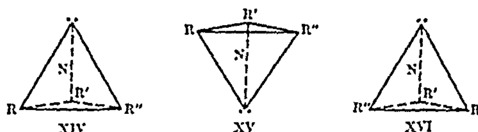
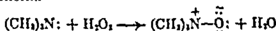


Figure 21 • Racemization of Tertiary Amine

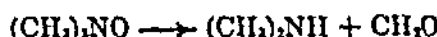
In the case of a tertiary amine XIV, this would result in the formation of XV, which, when rotated through an angle of 180° is XVI. This is seen to be the mirror image of XIV. This is believed to be the explanation of the nonexistence of optically active tertiary amines, for racemization is too rapid to permit the isolation of an active isomer.

Amine Oxides. Trimethylamine oxide is formed by the action of hydrogen peroxide and some other oxidizing agents on trimethylamine (p. 359). The reaction is general.



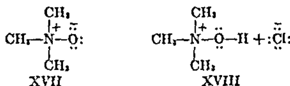
$$(CH_3)_3N: + H_2O_2 \longrightarrow (CH_3)_3\overset{+}{N}-\ddot{\underset{\cdot\cdot}{O}}: + H_2O$$

This oxide melts at 208° and is very hygroscopic. The aqueous solution of the oxide is basic and the compound crystallizes from this as a dihydrate, $(CH_3)_3NO \cdot 2H_2O$. It forms stable salts with acids, for example, $(CH_3)_3NO \cdot HCl$ is trimethylamine oxide hydrochloride. Heating the oxide or a salt causes decomposition to dimethylamine and formaldehyde.

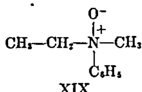


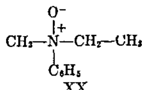
$$(CH_3)_3NO \longrightarrow (CH_3)_2NH + CH_2O$$

The free base has structure XVII, and the hydrochloride, XVIII.

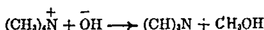


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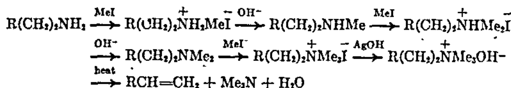
Pyrolysis of Quaternary Ammonium Bases. Tetramethylammonium hydroxide when heated decomposes to trimethylamine and methanol



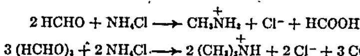
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This is a general method for degradation of amino compounds, and has been valuable in structural determination of naturally occurring bases, especially of alkaloids (Chap. 45). Any primary amine, RCH_2NH_2, can be converted into the quaternary ammonium base by **exhaustive methylation,** *i.e.*, by alternate reactions with methyl iodide and base to the quaternary ammonium iodide, then with silver oxide; or more simply with a mixture of methyl iodide and silver oxide. In this case the silver oxide converts the first addition compound at once to the free methylated amine (p. 351), which then undergoes further methylation.



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The first is essentially a dismutation reaction, for one mole of formaldehyde is oxidized to formic acid, and another is reduced to the stage of methanol. Some dimethylamine salt is formed also. The second reaction also involves oxidation and reduction.

Methylamine is a gas, very soluble in water (Table 69, p. 354) and has an odor closely like that of ammonia. Trimethylamine also is a gas very soluble in water. The odor is characteristically fishlike. It and dimethylamine are formed in the decaying of fish, and are present in herring brine, the fishy odor of which is due largely to trimethylamine.

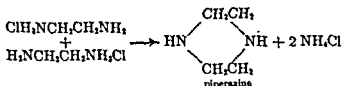
Diamines. In older nomenclature the name of the bivalent radical appears. In the I.U.C. system they are diaminoalkanes or, preferably, alkanediamines. Thus $H_2N—CH_2—CH_2—NH_2$ is ethylene diamine, 1,2-diaminoethane, or ethane-1,2-diamine

In general these compounds are very soluble in water. The first member is insoluble in hydrocarbon solvents and in ether. The simplest diamine, ethylenediamine is produced commercially by heating ethylene chloride under pressure with a large excess of ammonia.



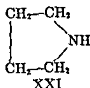
$$4\,NH_3 + ClCH_2CH_2Cl \longrightarrow NH_2CH_2CH_2NH_2 + 2\,NH_4Cl$$

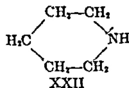
When the hydrochloride of ethylenediamine is heated, the cyclic compound piperazine is formed.



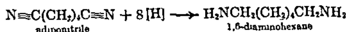
Higher diamines can be prepared by the reaction of the corresponding dibromide with potassium phthalimide or by reduction of the nitrile of a dibasic acid. In the putrefaction of proteins two diamines are formed, **putrescine**, tetramethylenediamine, $H_2N(CH_2)_4NH_2$, and **cadaverine**, pentamethylenediamine, $H_2N(CH_2)_5NH_2$. They result from the decarboxylation of the respective amino acids, ornithine, $H_2N(CH_2)_3CH(NH_2)COOH$, and lysine, $H_2N(CH_2)_4CH(NH_2)COOH$.

Both pentamethylenediamine and hexamethylenediamine dihydrochlorides, when heated, lose a molecule of ammonium chloride to form cyclic compounds, the hydrochlorides of pyrrolidine, XXI, and piperidine, XXII, respectively.





Hexamethylenediamine, $H_2N(CH_2)_6NH_2$. This is produced by reduction of adiponitrile.

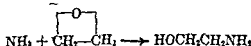


$$N{\equiv}C(CH_2)_4C{\equiv}N + 8\,[H] \longrightarrow H_2NCH_2(CH_2)_4CH_2NH_2$$

adiponitrile — 1,6-diaminohexane

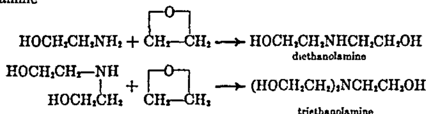
The diamine is important in the manufacture of "nylon" (p. 381).

Alkanolamines; Aminoalcohols. When ethylene oxide reacts with ammonia, the first product is ethanolamine, $HOCH_2CH_2NH_2$.



$$NH_3 + \overbrace{CH_2—CH_2}^{O} \longrightarrow HOCH_2CH_2NH_2$$

The product can react with more of the oxide, producing diethanolamine and triethanolamine

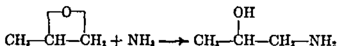


Ethanolamine is the main product when ammonia is in good excess (5 moles to 1), and triethanolamine when the oxide is in excess.

The ethanolamines are basic liquids, miscible with water and alcohol, insoluble in petroleum hydrocarbons and in ether. They have basic properties and form salts with acids. The respective boiling points for the mono-, di-, and triethanolamines are: 171°, 217° (150 mm.), 277° (150 mm.).

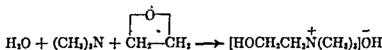
Ethanolamines are used for absorbing carbon dioxide and hydrogen sulfide from gases. These may be recovered from the solution by suitable heat treatment. Soaps made with ethanolamines and fatty acids are soluble in organic solvents; the oleate is even soluble in paraffin oil, and often is incorporated in this for the production of oil-in-water emulsions, such as those used as orchard sprays. The oleate also finds application in dry cleaning.

Propylene oxide reacts similarly to ethylene oxide. The reaction usually proceeds so that the hydroxyl group is on the secondary carbon atom (p. 242), with formation of 1-amino-2-propanol (isopropanolamine).



Quaternary Ammonium Compounds. A number of naturally occurring compounds of this type are of interest to the biochemist and organic chemist.

Choline, $[HOCH_2CH_2\overset{+}{N}(CH_3)_3]\overset{-}{O}H$. This is present in many organs of the body and is a constituent of lecithin, present in most plant and animal cells and thus widely distributed. Choline has been synthesized. A convenient method is the reaction of ethylene oxide and trimethylamine.



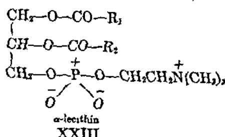
Choline is a viscous, hygroscopic liquid which decomposes when heated in aqueous solution to ethylene glycol and trimethylamine. It produces a drop in blood pressure.

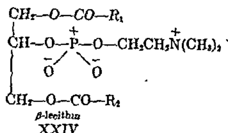
Acetylcholine, $[CH_3COO(CH_2)_2\overset{+}{N}(CH_3)_3]\overset{-}{O}H$. This is a very important substance physiologically. It lowers blood pressure when administered by subcutaneous or intramuscular injection; its activity is 1000 times that of choline. Whenever a parasympathetic nerve ending is stimulated acetylcholine is liberated.

Neurine $[CH_2{=}CH\overset{+}{N}(CH_3)_3]\overset{-}{O}H$. This is formed by the putrefaction of choline It can be obtained from choline by dehydration. It is very poisonous.

Lecithins. The brain and the yolk of eggs are especially rich in lecithin, which is present in most cells. It is a phospholipid. These are diesters of phosphoric acid in

which one ester linkage is with *glycerol or a glycol, the other with* an amino alcohol. In *lecithin* the amino alcohol is choline. Lecithins are widely distributed in plants and animals and are of great physiological importance. The two types are designated *α-lecithins*, XXIII, and *β*-lecithins, XXIV.


α-lecithin
XXIII


β-lecithin
XXIV

The third hydroxyl group *of phosphoric acid is not free but is neutralized by the* quaternary base. On hydrolysis the lecithin molecule *yields two molecules of higher fatty* acids (palmitic, stearic, oleic) and one molecule each of glycerol, phosphoric acid, and choline. There are many lecithins, because R_1CO and R_2CO may represent a number of different fatty acid residues.

In other phospholipids choline may be replaced by ethanolamine (colamine) or by *some other* aminoalcohol. A well-balanced diet must contain choline or lecithin, otherwise the liver does not *function normally.*

Identification of Amines. [illegible] substance may, among other [illegible] ally is a solid; if the former, it may be a solid, liquid, or gas, but [illegible] liquid. The ability to form a salt with an acid is a characteristic property of the free amine. This is readily apparent if the amine is but slightly soluble in water, because it goes into solution when a suitable *dilute aqueous acid, hydrochloric acid,* for example, is added. If the amine is water soluble, it may be titrated with a strong acid. Primary and secondary amines may be distinguished from tertiary through the formation of acyl derivatives by the action of acetyl chloride or, better, benzoyl chloride (Chap. 35). Primary amines may be distinguished from secondary amines by cold aqueous sodium nitrite and hydrochloric acid (p. 357).

Individual amines, if primary or secondary, may be identified by the melting points of solid derivatives, usually amides. Useful solid derivatives of tertiary amines usually are addition compounds, *such as the salts with hydrohalic acids, or the chloroplatinates.*

PROBLEMS

1. Starting with methyl alcohol, show reaction steps for the preparation of the following, reasonably free of other compounds.

a) methylamine
b) dimethylamine
c) trimethylamine
d) N-acetyldimethylamine
e) *dimethylnitrosoamine*
f) trimethylamine oxide
g) tetramethylammonium iodide
h) N-methylformamide

2. Starting with *n*-propyl alcohol as the only organic compound, show the steps by which the following may be prepared conveniently in the laboratory, but not necessarily pure.

a) *n*-propylamine (3 methods)
b) di-*n*-propylamine (2 methods)
c) tri-*n*-propylamine (2 methods)
d) di-*n*-propylnitrosoamine
e) tri-*n*-propylamine oxide
f) tetra-*n*-propylammonium bromide
g) *n*-butylamine
h) *n*-propyl-*n*-butylamine
i) 1-amino-2-propanol
j) N-propionyl-di-*n*-propylamine
k) 1-(N-propylamino)-2-propanol
l) 1-(N-*n*-butylamino)-2-propanol

3. Show how 3-aminopentane may be obtained from:

a) 3-pentanone
b) 3-pentanol
c) propionic acid
d) 1-propanol
e) diethylacetic acid
f) malonic ester and ethanol
g) silver nitrite and an organic compound
h) silver cyanide and an organic compound

4. Show how putrescine may be obtained from:

a) ethylene bromide
b) succinic acid
c) adipic acid
d) glutaric acid
e) 1,4-butanediol
f) butanedial
g) 1,4-dinitrobutane
h) ethylene glycol

5. Show how the following may be separated (stating reagent, conditions, and separation procedure), so as to obtain one compound in good yield and reasonably free of the other. Assume that no reaction, with the possible exception of salt formation, has taken place at the start of the separation.

a) *n*-butylamine and ethyl alcohol
b) *n*-amylamine and formic acid
c) di-*n*-propylamine and *n*-butyl alcohol
d) [illegible]
e) [illegible]
f) *n*-amylamine and *n*-amyl chloride
g) di-*n*-propylamine and *n*-propyl alcohol
h) *n*-amylamine and di-*n*-propylamine
i) triethylamine and *n*-butylamine
j) triethylamine and ethyl alcohol
k) di-*n*-propylamine and formic acid
l) *n*-propylamine and acetone
m) *n*-propylamine and methylene chloride
n) *n*-butylamine and carbon tetrachloride
o) diethylamine and ethyl alcohol
p) diethylamine and *n*-butylamine
q) diethylamine and carbon tetrachloride

6. Describe a convenient chemical test, stating reagent, conditions, solvent if any, and readily detectable change, which serves to distinguish between:

a) *n*-butylamine and di-*n*-butylamine
b) di-*n*-butylamine and tri-*n*-butylamine
c) *n*-butylamine and diethylamine
d) *n*-amylamine and di-*n*-propylamine
e) *n*-butylamine and triethylamine
f) N,N-dichloroethylamine and diethylammonium chloride
g) N-chlorodiethylamine and diethylammonium chloride
h) ammonium chloride and methylammonium chloride
i) *triethylamine and triethylamine oxide*
j) di-*n*-propylamine and di-*n*-propylnitrosamine
k) tri-*n*-propylamine and tri-*n*-propylamine oxide
l) di-*n*-propylnitrosoamine and tri-*n*-propylamine oxide
m) ammonium bromide and dimethylammonium bromide
n) N,N-dimethylethanolamine and trimethylamine oxide
o) di-*n*-amylamine and di-*n*-amylnitrosamine
p) ammonium iodide and di-*n*-butylammonium iodide
q) *n*-butylammonium chloride and tri-*n*-butylammonium chloride

7. Compound *A*, $C_4H_{11}N$, gives compound *B*, $C_6H_{13}ON$, with acetic anhydride and *C*, $C_4H_{10}O$, with cold aqueous sodium nitrite and hydrochloric acid. *Write possible structures for A.*

8. *Compound A*, $C_4H_{12}NCl$ dissolves readily in water. Addition of sodium nitrite to the resulting solution and ether extraction of this gives compound *B*, $C_4H_{10}ON_2$. Write possible structures for *A*.

9. Compound *A*, $C_6H_{15}N$, gives *B*, $C_6H_{15}ON$, with hyurogen peroxide. Write possible structures for *A*.

10. Compound *A*, $C_5H_{13}N$, gives *B*, $C_7H_{15}ON$, with acetic anhydride, and *C*, $C_5H_{12}O$, with sodium nitrite and hydrochloric acid. This when heated with chromic acid mixture gives *D*, $C_5H_{10}O_2$. All possess optical activity. Write possible structures for *A*.

11. Compound *A*, $C_5H_{13}N$, gives *B*, $C_7H_{15}ON$, with acetic anhydride, and *C*, $C_5H_{12}ON_2$, with cold hydrochloric acid and sodium nitrite. All possess optical activity. Write possible structures of *A*.

•12. Compound *A*, $C_8H_{15}N$, slightly soluble in water and dilute aqueous base, dissolves [illegible]

drawn from these statements? Show how they lead to a probable structure for *A*. Are other structures possible?

13. Compound *A*, $C_5H_{13}ON$ gives *B*, $C_9H_{17}O_3N$, with acetic anhydride and *C*, $C_5H_{12}O_2$, [illegible] acid and sodium nitrite. When *C* is heated with alkaline perman- [illegible] This when heated is converted to [illegible] deductions can be drawn from these statements? Show how they lead to a probable structure for *A*.

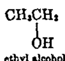
14. Compound *A*, $C_8H_{19}N$, slightly soluble in water and dilute aqueous base, dissolves *readily in dilute hydrochloric acid. A reacts with methyl iodide to give B*, $C_9H_{22}NI$, and this with silver oxide gives *C*, $C_9H_{23}ON$. When *C* is heated, a gas is evolved, and when this *is passed* into cold water an organic liquid, *D*, is obtained, 3-methyl-1-pentene, free of any isomer. What deductions *can* be *drawn from these* statements? *Show how they lead* to a probable structure *for A*.

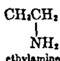
15. Compound *A*, $C_{10}H_{23}N$, gives *B*, $C_{12}H_{25}ON$ with acetic anhydride, and $C_{10}H_{22}ON_2$ with cold hydrochloric acid and sodium nitrite. There are 3 and only 3 stereoisomeric forms of *A*. Write a possible structure of *A*. Are other structures possible?

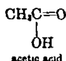
CHAPTER 22

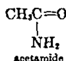
Amides

Amides bear the same relationship to amines that acids bear to alcohols; amines and amides have an amino group where alcohols and acids have the hydroxyl group. Whereas amines, like alcohols, have alkyl radicals, amides, like acids, have acyl radicals.

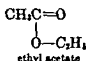

ethyl alcohol

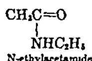

ethylamine


acetic acid

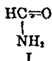

acetamide

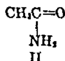
Thus amides are acylated ammonias (acyl derivatives of ammonia). Corresponding to secondary and tertiary amines are secondary and tertiary amides; however, these are relatively unimportant. Corresponding to esters are N-alkylated amides.

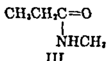

ethyl acetate

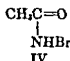

N-ethylacetamide

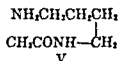
Nomenclature. Amides are named from the corresponding acids to which they are transformed on hydrolysis. Thus I is formamide, II is acetamide. When a substituent is attached to the nitrogen atom, it is so indicated. Thus III is N-methylpropionamide and IV is N-bromoacetamide.


I


II

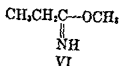
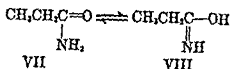

III


IV


V

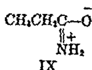
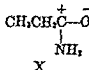
In the I.U.C. system the amide group is named as a substituent, especially when some other functional group is present. Thus II is carbamidomethane ($-CONH_2$ is carbamido), III is methylcarbamidoethane or, better, propionamidomethane, and V is 4-acetamido-1-aminobutane ($CH_3CO-NH-$ is acetamido).

Structure. Two types of derivatives of amides are known, *viz.*, the N-alkyl derivatives, which have the amide structure, III, and the O-alkyl derivatives, which have the imide structure, VI.

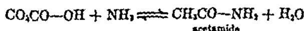
Isomeric with III is methyl imidopropionate (propionimidomethyl ester, propionimidomethyl ether), VI. Some experimental evidence has been interpreted as indicating that there may be a dynamic equilibrium between tautomeric forms of amides, as shown by VII and VIII. Amides often react in tautomeric forn..

There are resonance forms of the amide and imide structures. Those of the amide structure are VII, IX, and X.

General Methods of Preparation. The most economical method is decomposition of the ammonium salt of the acid, and the one which usually offers least difficulty in purification is ammonolysis of the ester.

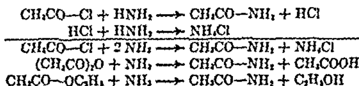
1. *Pyrolysis of ammonium salts of acids; ammonolysis of acids.* When ammonium acetate is heated (in a sealed tube, to prevent loss by volatilization) it is slowly transformed to acetamide.



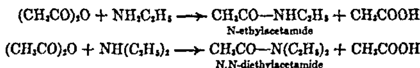
The reaction is slow, and an equilibrium is reached. The acid is 75 and 85 per cent converted at 125° and 212°, respectively, with one mole of ammonia. The existence of an equilibrium is normal, in view of the small value of ΔH, *viz.*, +1.9 kcal., as calculated from bond energies. Actually the reaction involves ammonium ion, rather than ammonia. In an excess of acetic acid the reaction can be carried out at atmospheric pressure, and water can be removed as formed by slow distillation of the acid.

By passage of ammonia and acid in the vapor phase over hot dehydration catalysts (alumina, etc.), amides can be formed. The conditions must be controlled carefully to prevent formation of nitriles (p. 389).

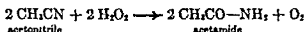
2. *By ammonolysis of acyl halides, anhydrides, or esters.* Acyl halides react exothermically, sometimes with explosive violence; anhydrides react readily, esters slowly (p. 215).



A mono- or di-N-alkylated amide is obtained when ammonia is replaced by a secondary or tertiary amine.



3. *By hydration of nitriles.* Under mild conditions nitriles hydrate to amides (p. 391).



One of the most convenient methods is hydrogen peroxide in dilute aqueous alkali at 40°.

Physical Properties of Amides. Amides unsubstituted at the amino group are solids with the exception of formamide (Table 71). They boil much

TABLE 71 | **Constants of Some Normal Amides**

NAME	FORMULA	M.P. °C	B.P. °C	SOLUB. IN H_2O G./100 G.	DIELECT. CONST.	DIPOLE MOMENT
Formamide	$H{-}CONH_2$	2.5	200 [d]	misc.	84	3.2
Acetamide [a]	$CH_3{-}CONH_2$	82 3	221.2	238	60 [b]	3.6
Propionamide	$C_2H_5{-}CONH_2$	79 5	213	v. sol.		
Butyramide	$C_3H_7{-}CONH_2$	116	216	v. sol.		
Valeramide	$C_4H_9{-}CONH_2$	106	232	sol.		3.7
Caproamide	$C_5H_{11}{-}CONH_2$	101	255	s. sol.		3.9

[a] K_a at 25°, 8.3×10^{-16}; K_b at 25°, 3×10^{-15}. [b] At 80°. [d] Decomposes.

higher than the corresponding acids, in fact, higher than any other compounds of the same number of carbon atoms having but one functional group. It is seen from Table 11, page 28, that formamide has a dipole moment of 3.2 *D.*, and from Table 12, page 30, a dielectric constant of 84, values near the top for covalent compounds. Thus from the dipole moment alone a rather high boiling point would be expected (Table 13, p. 31); the high dielectric constant would be expected to have a similar effect. The considerable degree of association connected with hydrogen bonding is partly responsible for the high dielectric constant and high boiling point.

Amides are very soluble in water and the lower members are insoluble in alkanes. In the fused state, formamide and acetamide are good ionizing solvents and dissolve many inorganic salts.

Reactions of Amides. In general these are related to ammonia, as in the case of amines (p. 355). The nitrogen-to-carbon bond of amides is cleaved more easily than that of amines.

1. *Acid and base properties.* In Table 72 are shown the K_a and K_b values of a number of derivatives of ammonia.

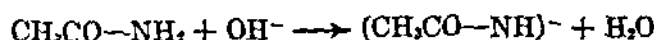
Whereas an alkyl radical does not greatly change the basic character of ammonia, an acyl radical greatly reduces it, and at the same time increases the acidic character. Thus acetamide is at the same time a very weak acid and a very weak base.

TABLE 72 | **Effect of Substituents on Acidity and Basicity of Ammonia**

NAME	FORMULA	K_a	K_b
Ammonia	NH_3	10^{-33}	1.8×10^{-5}
Ethylamine	$CH_3CH_2NH_2$	[a]	5×10^{-4}
Diethylamine	$(CH_3CH_2)_2NH$	[a]	1×10^{-3}
Triethylamine	$(CH_3CH_2)_3N$	[b]	6×10^{-4}
Acetamide	CH_3CONH_2	8.3×10^{-16}	3.1×10^{-15}
Diacetamide	$(CH_3CO)_2NH$	[c]	
Triacetamide	$(CH_3CO)_3N$		

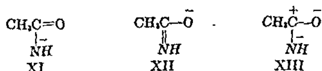
[a] Forms potassium ethylamide (or potassium diethylamide) with metallic potassium.
[b] Not acidic, since it lacks a hydrogen atom attached to nitrogen.
[c] Probably about 10^{-11}.

With a strong base an amide reacts only slightly in aqueous solution to form a salt.



$$CH_3CO{-}NH_2 + OH^- \longrightarrow (CH_3CO{-}NH)^- + H_2O$$

As in the case of sodio acetoacetic ester (p. 329) the negative ion is a resonance hybrid. In this case there are three, as in the case of the amide, *i.e.*, XI, XII, and XIII.



The negative ion, although present to only a slight extent in dilute aqueous solution, is important in base-catalyzed reactions of amides, for example, hydrolysis. Acetamide forms a mercuric salt with mercuric oxide.



$$2\,CH_3CO{-}NH_2 + HgO \longrightarrow (CH_3CO{-}NH)_2Hg + H_2O$$

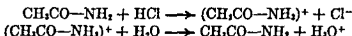
This compound is not ionized and is colorless. The reaction sometimes is used as a test for an amide. Freshly precipitated yellow mercuric oxide changes to a colorless solid on the addition of an amide. Diacetamide and alcoholic potash give potassium diacetamide.



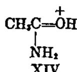
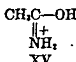
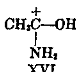
$$(CH_3CO)_2NH + KOH \rightleftharpoons (CH_3CO)_2NK + H_2O$$

With a strong acid an amide reacts only slightly in aqueous solution. However, a salt can be formed in the absence of water, as for example, by

passing dry hydrogen chloride into an ether solution of acetamide, to obtain an insoluble hydrochloride. This is largely hydrolyzed when added to water.



In the positive ion the third proton may be attached to either the nitrogen atom or the oxygen atom. There probably is tautomerism between the two. For the ion in which the third proton is attached to oxygen, three resonance forms can be written, *viz.*, XIV, XV, and XVI.

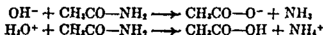




The contribution of XVI to the structure of the positive amide ion is more important than the contribution of X (p. 370) to the structure of the amide. Thus there is a greater positive charge on the carbon atom of the positive ion, and this promotes reactions with nucleophilic reagents such as alcohol and water (refer to Aldehydes and Ketones, p. 261). This ion is important in many acid-catalyzed reactions of amides, for example, hydrolysis.

2. *Hydrolysis of amides.* This is the most important reaction of amides. When acetamide is boiled with water, it hydrolyzes very slowly to acetic acid and ammonia.



This is the reverse of one reaction for the preparation of amides (p. 370). The hydrolysis reaction is accelerated by the presence of hydroxyl or hydronium ions, which first convert the amide to an ion, XI or XIV, respectively. These are more reactive than acetamide itself. Acetamide is hydrolyzed about seven times as rapidly by a strong base as by a strong acid at equivalent concentration. The base or acid prevents the reverse reaction by combining with one of the products.



Even the catalyzed reaction is not fast. It is much slower than hydrolysis of esters. Branching of the carbon chain at the α-position causes marked retardation of the reaction, as in the case of esters. A nonreactive amide usually will react when heated to 150° with orthophosphoric acid.

3. *Reaction with nitrous acid.* The amino group is replaced by the hydroxyl group in a reaction with hydrochloric acid and sodium nitrite. The acid concentration must be higher than with amines to obtain sufficient concentration of the protonated intermediate.



The reaction is useful when hydrolysis is slow.

4. *Acylation.* Heating with acyl halides or anhydrides results in formation of diamides.

$$CH_3CO{-}NH_2 + Cl{-}COCH_3 \longrightarrow \underset{\text{diacetamide}}{(CH_3CO)_2NH} + HCl$$

5. *Reaction with halogen.* Under alkaline conditions substitution takes place rapidly at the nitrogen atom, bromine, for example, forming N-bromoacetamide and N,N-dibromoacetamide (acetobromamide and acetodibromamide).

$$Br_2 + NaOH + CH_3CONH_2 \longrightarrow CH_3CONHBr + NaBr + H_2O$$
$$2\,Br_2 + 2\,NaOH + CH_3CONH_2 \longrightarrow CH_3CONBr_2 + 2\,NaBr + 2\,H_2O$$

The halogen atom in compounds of this type, like that in N-halogenated amines is so-called "positive" halogen, for it does not precipitate silver halide on the addition of silver ion and reacts with the corresponding hydrogen halide to regenerate the halogen, or with hydrogen iodide to form iodine.

$$HBr + CH_3CONHBr \longrightarrow CH_3CONH_2 + Br_2$$
$$2\,HI + 2\,CH_3CONHBr \longrightarrow CH_3CONH_2 + I_2 + 2\,HBr$$

N-Bromoacetamide can be a convenient source of hypobromous acid in the presence of water.

$$CH_3CONHBr + H_2O + \underset{\text{2-butene}}{CH_3CH{=}CHCH_3} \longrightarrow \underset{\text{3-bromo-2-butanol}}{CH_3CHOH{-}CHBrCH_3} + CH_3CONH_2$$

6. *The Hofmann degradation.* This is an important method for the preparation of lower primary amines. It involves heating the N-bromoamide with a base in aqueous or alcoholic solution.

$$3\,NaOH + \underset{\text{N-bromoacetamide}}{CH_3CONHBr} \longrightarrow \underset{\text{methylamine}}{CH_3NH_2} + Na_2CO_3 + NaBr + H_2O$$

The first step is a molecular rearrangement leading to the formation of an isocyanate, which readily undergoes hydrolysis under basic conditions to the amine (p. 395).

$$NaOH + CH_3CONHBr \longrightarrow \underset{\text{methyl isocyanate}}{CH_3N{=}C{=}O} + H_2O + NaBr$$
$$2\,NaOH + CH_3N{=}C{=}O \longrightarrow CH_3NH_2 + Na_2CO_3$$

Proof that isocyanate is an intermediate is given by carrying out the reaction in absolute alcohol.

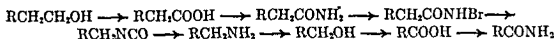
$$C_2H_5ONa + CH_3CONHBr \longrightarrow CH_3N{=}C{=}O + C_2H_5OH + NaBr$$
$$\underset{\text{methyl isocyanate}}{CH_3N{=}C{=}O} + C_2H_5OH \longrightarrow \underset{\text{N-methylurethane}}{CH_3NH{-}CO{-}OC_2H_5}$$

The formation of N-methylurethane ($NH_2{-}CO{-}OC_2H_5$ = urethane) results from the reaction of the isocyanate with alcohol (p. 396).

The Hofmann degradation is a general reaction, except that higher amides (above *n*-heptyl) give mainly nitriles, due to formation of dibromoderivatives.

$$RCH_2CONBr_2 \longrightarrow RC{\equiv}N + 2\,HBr$$

It is possible to degrade higher amides to lower amides, or higher alcohols to lower alcohols, or "build down," as this change is called sometimes.



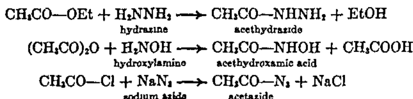
$$RCH_2CH_2OH \longrightarrow RCH_2COOH \longrightarrow RCH_2CONH_2 \longrightarrow RCH_2CONHBr \longrightarrow RCH_2NCO \longrightarrow RCH_2NH_2 \longrightarrow RCH_2OH \longrightarrow RCOOH \longrightarrow RCONH_2$$

However, a complication here is the formation of a secondary, as well as a primary alcohol (p. 358)

HYDRAZIDES, HYDROXAMIC ACIDS, AND AZIDES

These are amide type compounds. They differ from amides in being related, respectively, to hydrazine, hydroxylamine, and hydrazoic acid, instead of to ammonia.

Preparation. Hydrazides and hydroxamic acids are obtained from hydrazine or hydroxylamine, respectively, by a reaction with an ester, anhydride, or acyl chloride. An azide is obtained by the action of an acyl chloride with sodium azide.

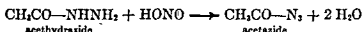


$$\underset{}{CH_3CO{-}OEt} + \underset{\text{hydrazine}}{H_2NNH_2} \longrightarrow \underset{\text{acethydrazide}}{CH_3CO{-}NHNH_2} + EtOH$$

$$(CH_3CO)_2O + \underset{\text{hydroxylamine}}{H_2NOH} \longrightarrow \underset{\text{acethydroxamic acid}}{CH_3CO{-}NHOH} + CH_3COOH$$

$$CH_3CO{-}Cl + \underset{\text{sodium azide}}{NaN_3} \longrightarrow \underset{\text{acetazide}}{CH_3CO{-}N_3} + NaCl$$

Azides are prepared also by the action of nitrous acid on hydrazides.



$$\underset{\text{acethydrazide}}{CH_3CO{-}NHNH_2} + HONO \longrightarrow \underset{\text{acetazide}}{CH_3CO{-}N_3} + 2\,H_2O$$

Like amides, these three types of compounds undergo hydrolysis with aqueous acids to form the organic acid and the respective nitrogen analog of ammonia. Hydrazides and azides undergo basic hydrolysis also. Hydrazides in general resemble amides as regards solubility and are more resistant to hydrolysis.

Hydrazides, like hydrazine, reduce ammoniacal silver and hot Fehling's solution. An especially interesting reaction is the formation of azides with nitrous acid.

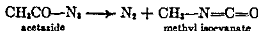
Hydroxamic acids are useful intermediates in testing for esters, anhydrides, acyl halides, and amides, all of which are easily converted to the respective hydroxamic acid, merely on heating with hydroxylamine. Hydroxamic acids give an intense red (sometimes brown) color with ferric ion as a result of the formation of a ferric hydroxamate.



$$3\,CH_3CO{-}NHOH + FeCl_3 \rightleftharpoons \underset{\text{red}}{(CH_3CO{-}NHO)_3Fe} + 3\,HCl$$

The test can be extended to acids and alcohols, since these easily form esters.

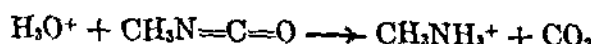
Azides are not very stable and decompose when heated. This is an interesting reaction, for nitrogen is eliminated and an isocyanate is formed.



$$\underset{\text{acetazide}}{CH_3CO{-}N_3} \longrightarrow N_2 + \underset{\text{methyl isocyanate}}{CH_3{-}N{=}C{=}O}$$

The alkyl group originally attached to carbon is now attached to a nitrogen atom. A molecular rearrangement is involved in this reaction, a change somewhat similar to the one accompanying the Hofmann degradation. This reaction is called the Curtius rearrangement. In this the isocyanate is easily obtained, for the reaction usually is carried out in benzene solution, thus avoiding the presence of water. The

reaction is more easily controlled than is the Hofmann degradation *and is preferred in* research. When the isocyanate is heated with aqueous acids, the salt of a primary amine is obtained.



$$H_3O^+ + CH_3N{=}C{=}O \longrightarrow CH_3NH_3^+ + CO_2$$

AMIDES OF DIBASIC ACIDS

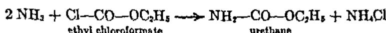
There are two types of amides of dibasic acids, *viz*, the monoamides, which have one carboxyl and one carbamido group, and the diamides, which have two carbamido groups. Although carbonic acid is not a dicarboxylic acid and is itself unstable, its diamide, urea, is stable; and its monoamide, carbamic acid, although unstable, is known in the form of derivatives and salts.

Carbamic Acid, NH_2COOH. The ammonium salt is formed by the direct union of carbon dioxide and ammonia, either in the gas phase or, better, in a nonaqueous solvent such as alcohol under cooling.



$$O{=}C{=}O + 2\,NH_3 \longrightarrow NH_2{-}CO{-}\overset{-}{O}\cdots\overset{+}{N}H_4$$

Ethyl carbamate, *urethane, is obtained by the action of ammonia on ethyl chloroformate*, or on ethyl carbonate (but in lower yield).

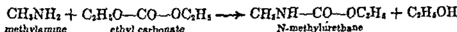


$$2\,NH_3 + \underset{\text{ethyl chloroformate}}{Cl{-}CO{-}OC_2H_5} \longrightarrow \underset{\text{urethane}}{NH_2{-}CO{-}OC_2H_5} + NH_4Cl$$



$$NH_3 + C_2H_5O{-}CO{-}OC_2H_5 \longrightarrow NH_2{-}CO{-}OC_2H_5 + C_2H_5OH$$

If an amine replaces ammonia, the product is a substituted urethane.



$$\underset{\text{methylamine}}{CH_3NH_2} + \underset{\text{ethyl carbonate}}{C_2H_5O{-}CO{-}OC_2H_5} \longrightarrow \underset{N\text{-methylurethane}}{CH_3NH{-}CO{-}OC_2H_5} + C_2H_5OH$$

Urea, Carbamide, $CO(NH_2)_2$. This was discovered in urine in 1773. It is a *white solid melting at 132°, is very soluble in water, slightly soluble in alcohol*, and insoluble in ether. It is the final metabolic product of most of the nitrogenous food consumed by humans, is present in low concentration in the body fluids, and is removed from the blood by the kidneys. An adult excretes 25 to 30 grams per day.

Urea may be obtained from urine, after concentration to a small volume, by adding concentrated nitric acid, which throws down the sparingly soluble nitrate, $O{=}C(NH_2)_2 \cdot HNO_3$. This is dissolved in water, the color of the solution is discharged by adding permanganate, the nitric acid is removed by adding barium carbonate, the mass is evaporated to dryness, and the urea is extracted with alcohol.

The classical synthesis of urea by Wöhler in 1828 from ammonium sulfate and potassium cyanate is now regarded as an important date in the history of organic chemistry, because it showed that a product of natural origin can be synthesized in the laboratory. He was expecting to obtain ammonium cyanate. The actual product, urea, results from ammonium cyanate.

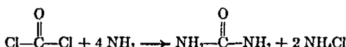


$$NH_4OCN \longrightarrow NH_2{-}CO{-}NH_2$$

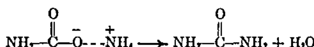
The reaction is somewhat reversible, for it has been observed that when silver ion is added to a hot aqueous urea solution, silver cyanate is precipitated.

Urea is prepared in other ways, which are all general methods for amide preparation (p. 370).

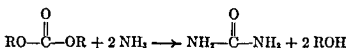
a) By the ammonolysis of carbonyl chloride (phosgene).

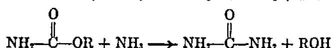


b) By heating ammonia and carbon dioxide under pressure at 140°, at which temperature ammonium carbonate decomposes like other ammonium salts do.

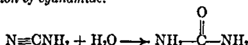


c) By the ammonolysis of alkyl carbonates and of urethane.





d) By the hydration of cyanamide.



Methods (*b*) and (*d*) are important in industry.

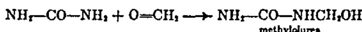
Urea ($K_b = 1.5 \times 10^{-14}$) is a much weaker base than ammonia and the amines but is stronger than acetamide (3.1×10^{-15}). It forms salts with strong acids and these, when slightly soluble like the nitrate (above) and the oxalate, $(COOH)_2 \cdot 2\,CO(NH_2)_2$, can readily be obtained by adding the acid to a concentrated aqueous solution of urea.

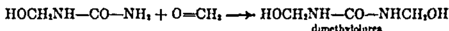
The most important reaction of urea is its hydrolysis to ammonium carbonate, in which reaction ammonia and carbon dioxide are evolved.



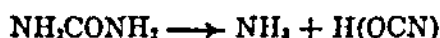
This change is accelerated by hydrogen or hydroxide ions. It is also brought about by the organism *Micrococcus ureae*, which causes the liberation of ammonia from urine when it is allowed to stand for some time. The enzyme which induces the change is called **urease**.

Urea reacts readily with formaldehyde.

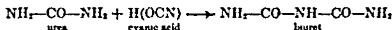




When heated above its melting point urea decomposes to ammonia and cyanic acid (p. 394).



Owing to the great reactivity of cyanic acid, other changes take place. If the temperature is not too high, cyanic acid reacts with urea to form biuret.

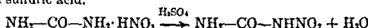


At higher temperatures cyanic acid is converted to cyanuric acid and cyamelide, and if heated high enough cyanuric acid depolymerizes to cyanic acid, which distils. Thus heating urea is a convenient method for obtaining cyanic acid.

Biuret in aqueous solution gives a characteristic violet-red color with copper sulfate and alkali. This is used as a test for urea. Other substances give somewhat similar colors as, for example, proteins.

Urea is manufactured in large quantities. It is an important nitrogen fertilizer, for which purpose it is almost ideal. It is used for the manufacture of the urea type of plastics (p. 282) and of barbituric acid and its derivatives.

Nitrourea, $NH_2CONHNO_2$. This is obtained when urea nitrate is added to cold concentrated sulfuric acid.



Nitrourea is a solid, melting at 159°, slightly soluble in water, unstable in hot water. It is a somewhat stronger acid than acetic acid. On reduction, either electrolytically or by zinc and an acid, it is converted into semicarbazide.

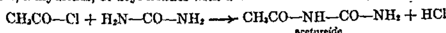


Semicarbazide, $H_2NCONHNH_2$. Besides the above method, this compound can be obtained from hydrazine and urea at 100°.

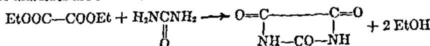


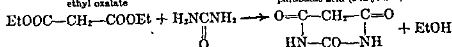
Like hydrazine, it reduces ammoniacal silver solution and hot Fehling's solution. It is useful in the detection and identification of aldehydes and ketones, with which it reacts readily to form slightly soluble and usually readily crystallizable semicarbazones (p. 271).

Ureides. These are acyl derivatives of urea. They may be obtained by the action of esters, anhydrides, or acyl halides with urea.



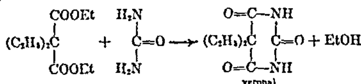
With esters of some dibasic acid, as for example oxalic, malonic, or substituted malonic acid, cyclic diureides are formed.





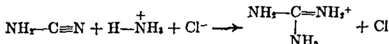
Parabanic acid is associated with the chemistry of uric acid, from which it was first obtained as a degradation product.

Barbituric acid is the parent substance of an important group of soporifics, the **barbiturates.** One of the best known is the diethyl derivative, veronal (barbital). Ethyl diethylmalonate is used in its preparation.

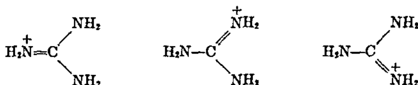


A large number of barbiturates are known, due largely to the ease of preparing derivatives of ethyl malonate (p. 331). Also one or both of the nitrogen atoms may hold a substituent group.

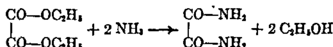
Guanidine, $HN{=}C(NH_2)_2$. This is related to urea in having the bivalent imine group, NH, in place of the oxygen atom. Its hydrochloride is obtained by heating an alcoholic solution of cyanamide with ammonium chloride at 100° (under pressure).



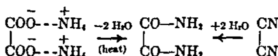
Guanidine is very soluble in water; the solution is strongly basic and absorbs carbon dioxide from the air. The replacement of the oxygen atom of urea by the imino group of guanidine brings about a surprisingly large increase in the basic character ($K_b = 3 \times 10^{-1}$ approx.). The strongly basic character of guanidine is due to the high stability of guanidinium ion, that is, to the pronounced tendency of guanidine to acquire a proton and pass into this ion. Guanidinium ion is highly stable because it can resonate among three equivalent electronic structures.



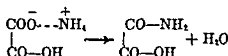
Oxamide, $(CONH_2)_2$. This forms rapidly when methyl or ethyl oxalate is shaken with concentrated aqueous ammonia.



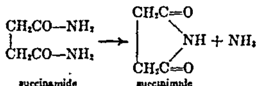
It is formed when ammonium oxalate is heated or when cyanogen undergoes hydration (p. 386).



Oxamide has a low solubility in water and sublimes at 180°, without melting and with partial decomposition into cyanogen and water. When acid ammonium oxalate is heated, **oxamic acid** is formed.



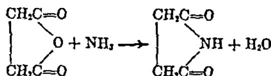
Succinamide, $(CH_2CONH_2)_2$. This is prepared from ethyl succinate and ammonia. It melts at 242 to 243° and decomposes into ammonia and succinimide at 200°.



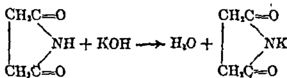
This recalls the formation of succinic anhydride on heating succinic acid.

IMIDES

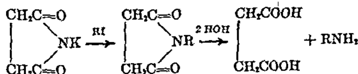
Imides are cyclic secondary amides. Succinimide is the best known saturated example, glutarimide next. The former has a five-membered ring, like succinic anhydride, the latter a six-membered ring. Imides with smaller rings are not very stable, and those with larger rings are formed with difficulty, owing to predominance of the bimolecular reaction. Succinimide and glutarimide may be obtained by passing a stream of ammonia over the heated acid or anhydride, or by heating the monoamide or diamide.



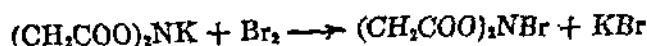
Succinimide is acidic ($K_a = 3 \times 10^{-11}$), as a result of the attachment of two acyl groups to the nitrogen atom. In alcoholic solution it reacts with potassium hydroxide to form **potassium succinimide.**



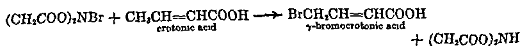
This reacts with high boiling alkyl halides (or with lower ones when heated under pressure) to yield N-substituted succinimides. These undergo hydrolysis to yield primary amines.



N-Bromosuccinimide is obtained by the action of bromine on potassium succinimide.

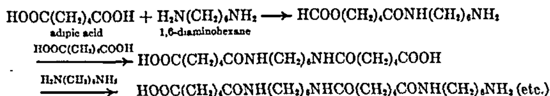


It is a solid (m p. 178°) and easily purified. It reacts with unsaturated compounds in a unique way. *Bromination* by substitution takes place on a carbon atom adjacent to an unsaturated carbon atom.



AMIDES OF DIAMINES

Within recent years the amide reaction between diamines and dibasic acids has [illegible]



$$HOOC(CH_2)_4COOH + H_2N(CH_2)_6NH_2 \longrightarrow HCOO(CH_2)_4CONH(CH_2)_6NH_2$$

adipic acid 1,6-diaminohexane

$$\xrightarrow{HOOC(CH_2)_4COOH} HOOC(CH_2)_4CONH(CH_2)_6NHCO(CH_2)_4COOH$$

$$\xrightarrow{H_2N(CH_2)_6NH_2} HOOC(CH_2)_4CONH(CH_2)_6NHCO(CH_2)_4CONH(CH_2)_6NH_2 \text{ (etc.)}$$

The compound resulting from the reaction of one mole each of acid and diamine can in turn react with more acid and/or diamine and the compound resulting can react with more diamine and/or acid. The reaction continues until a long, linear molecule is formed. Nylon is thus a polyamide of high molecular weight.

Detection and Identification of Amides. Amides, like esters, anhydrides, and acyl halides, give the ferric hydroxamate test (p. 375). When boiled with an aqueous or alcoholic solution of a strong base, amides are converted into volatile ammonia and a nonvolatile salt of the acid. Substituted amides give, instead of ammonia, primary or secondary amines, which like ammonia have an alkaline reaction and are volatile. Cyanides (nitriles) also give ammonia, while alkyl isocyanates give amines. Moreover, ammonium salts give ammonia, and amine salts give amines with *cold* alkali solutions. In carrying out the test, therefore, one must make sure that cold alkali is without action.

Detection of an acidic component of an amide usually can be realized by boiling with moderately concentrated (40–70%) sulfuric acid. A volatile acid will distil with the water. Nitriles react similarly, but isocyanates yield only carbonic acid.

Identification of the acidic and basic components obtained by hydrolysis of the amide is an aid in the identification of the amide. In general, amides have much higher melting and boiling points than cyanides and isocyanates.

PROBLEMS

1. Show the reaction steps for a preparation of *n*-amylamine, starting with:

a) *n*-amyl alcohol
b) *n*-hexyl alcohol
c) *n*-heptyl alcohol
d) *n*-valeric acid
e) hexanoic acid
f) heptanoic acid
g) *n*-valeraldehyde
h) methyl *n*-valerate
i) *n*-butyl alcohol
j) *n*-amyl *n*-valerate

2. Having *n*-propyl alcohol as the only organic compound (excepting sodium cyanide), show the sequence of operations (reagents and conditions) involved in obtaining:

a) propionamide (3 methods)
b) acetamide
c) 1-propionamidopropane
d) propionamidoethane
e) 1-propionamidobutane
f) 1-carbamidopropane
g) 3-carbamidoheptane
h) 3-carbamidohexane
i) 3-carbamidopentane
j) N-ethylacetamide
k) 1-acetamidopropane
l) 1-acetamidobutane
m) dipropionylamide
n) dipropionyl-*n*-propylamide
o) propionhydrazide (3 methods)
p) propionhydroxamic acid (3 methods)
q) propionazide
r) 1-propionamido-2-propanol

3. Having *n*-butyl alcohol as the only organic compound, show the sequence of operations (reagents and conditions) involved in obtaining:

a) *n*-butyramide
b) 1-*n*-butyramidobutane
c) 1-*n*-butyramidopropane
d) 2-*n*-butyramidopropane

e) n-valeramide
f) propionamide
g) 3-n-butyramido-2-butanol
h) ethylbarbituric acid
i) ethyl-n-butylbarbituric acid
j) n-butyrohydroxamic acid

4. Starting with ethyl malonate, and using any compounds desired, show steps for the preparation of:

a) acetamide
b) propionamide
c) n-butyramide
d) isobutyramide
e) ethylbarbituric acid
f) diethylbarbituric acid
g) n-amylbarbituric acid
h) allylbarbituric acid
i) methylamine
j) ethylamine
k) dimethylamine
l) triethylamine

5. Outline a practical laboratory preparation for the following, starting with ethanol, 1-propanol, 1-butanol and ethyl malonate as the only organic compounds:

a) n-caproamide
b) crotonamide
c) α-ethyl-n-butyramide
d) 3-aminopentane
e) N-ethylcrotonamide
f) α-methyl-n-butyramide
g) 3-ethylaminopentane
h) α-ethyl-n-valeramide
i) α-ethyl-n-caproamide
j) 3-aminohexane
k) 3-acetamidoheptane
l) α-methyl-n-valeramide
m) α-methyl-n-caproamide
n) 2-aminohexane
o) 2-propionamidobutane
p) 2-propionamidopentane
q) γ-methyl-n-butyramide
r) γ-methyl-n-valeramide

6. Describe a convenient chemical test (reagent, solvent if any, and readily detectable change) which serves to distinguish between:

a) propionamide and n-propylamine
b) propionamide and di-n-propylamine
c) propionamide and N-ethylpropionamide
d) propionamide and dipropionamide
e) propionamide and n-butyramide
f) propionamide and n-valeramide
g) propionamide and formamide
h) propionamide and propionhydrazide
i) propionamide and propionazide
j) propionamide and propionhydroxamic acid
k) propionamide and urea
l) propionamide and propionureide
m) propionamide and oxamide
n) propionamide and succinimide
o) propionamide and semicarbazide
p) propionamide and guanidine

7. Compound *A*, C_4H_7ON, dissolves readily in water to give a neutral solution. When its solution in 50% sulfuric acid is distilled slowly, an acidic distillate is obtained. When this is neutralized with slaked lime and the resulting solution is evaporated, a solid, *B*, remains. When this is heated, a liquid, *C*, is obtained, distilling at 101°, and only slightly soluble in water. What deductions can be drawn from these statements? Show how they lead to a probable structure for *A*.

8. Compound *A*, $C_4H_{10}O_2N_2$, is optically active. When heated, it is converted into *B*, $C_4H_7O_2N$. Write all possible formulas of *A*.

9. Compound A, $C_5H_{11}ON$, dissolves in water to give a neutral solution, B. A is only slowly altered by heating with aqueous acid or base, but with cold dilute sulfuric acid and sodium nitrite, a gas is evolved copiously. Steam distillation of the solution, after adjusting to pH3, gives an acidic distillate, C, which rotates the plane of polarized light. B does also. Write all possible formulas of A.

10. Compound A, $C_6H_{14}O_2N_2$, dissolved in water to give a neutral solution. On standing in dilute aqueous sulfuric acid the pH slowly rose. The solution was heated until reaction was finished, then cooled. Ammonium hydroxide was added to neutrality, then in excess. On shaking with ethyl ether two phases were obtained, aqueous phase B, and ether phase C. When ammoniacal silver nitrate was added to B a dark precipitate formed. C was shaken with dilute hydrochloric acid, giving solution D. On the addition of sodium nitrite to D, cold, a gas was evolved, giving solution E. When E was heated with nitric acid, oxides of nitrogen were evolved and a solid F, $C_6H_{10}O_4$, crystallized out. When this was heated with manganous carbonate, cyclopentanone distilled. What deductions can be drawn from these statements? Show how they lead to a structure for A.

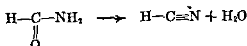
11. Compound A, $C_6H_{14}ON_2$, is slightly soluble in water and the solution, B, gives a dark precipitate with silver ion. With cold dilute hydrochloric acid and sodium nitrite, A is changed to C, $C_6H_{11}ON_3$. When C is heated, a gas is evolved and D is formed, $C_6H_{11}ON$. This when distilled with aqueous sodium hydroxide gives a basic aqueous distillate. Neutralization with hydrochloric acid, followed by evaporation, gives a solid, E, $C_5H_{14}NCl$. On the addition of sodium nitrite to a cold aqueous solution of E, a gas is evolved. On the addition of potassium dichromate and sulfuric acid, followed by heating, a green color develops and a two phase distillate is obtained. The lighter phase is diethyl ketone. What deductions can be drawn from these statements? Show how they lead to a structure for A.

CHAPTER 23

Derivatives of Hydrogen Cyanide

Among organic compounds classified as derivatives of hydrogen cyanide are: cyanides (nitriles), R—CN; isocyanides, R—NC; cyanates, R—OCN; isocyanates, R—NCO; thiocyanates, R—SCN; and isothiocyanates, R—NCS. There are other less important compounds, for example, cyanurates.

Hydrogen Cyanide, Hydrocyanic Acid, Prussic Acid, Formonitrile, HCN. This is formed when a strong acid is added to a solution containing cyanide ions, or to the cyanide of one of the stronger bases. It can be synthesized from the elements by passing a mixture of hydrogen gas and nitrogen gas through an electric arc between carbon poles. It is formed similarly from acetylene and nitrogen. It occurs in combination with benzaldehyde and glucose as the glucoside, amygdalin, in bitter almonds and in the kernels of some seeds, for example, peach, apricot, and plum. It can be obtained from formamide by heating with phosphorus pentoxide.

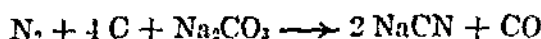


This reaction shows that hydrogen cyanide is the nitrile of formic acid.

Hydrogen cyanide is a very poisonous, very volatile liquid, b.p. 26°, miscible with water, alcohol, ether, etc. It can be expelled from aqueous solution by heating or by reducing the pressure. It is dried and passed into cylinders, where, as a liquid, it is easily transported. It is used as a fumigant, principally in ships and in orange groves, for extermination of pests. It was not a successful war gas in World War I, mainly because it is too volatile. The lethal dose for man is about $\frac{1}{20}$ gram.

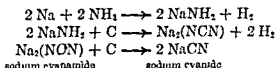
Hydrogen cyanide has a high dielectric constant and is a good ionizing solvent. It is a weak acid ($K_a = 1.3 \times 10^{-9}$). Its aqueous solution scarcely reddens litmus. It forms salts with strong bases but not with carbonates. Its salts are decomposed by carbon dioxide. The pure liquid is unstable; the addition of a small amount of hydrochloric acid stabilizes it. In water it decomposes slowly, partly to ammonium formate, partly to a brown amorphous substance.

Sodium Cyanide, NaCN. In the manufacture of this compound the important operation of fixation of nitrogen is accomplished. High temperatures are necessary. In the Bucher process, nitrogen is passed into a mixture of carbon, sodium carbonate, and iron turnings at 800 to 1000°. The iron acts catalytically.



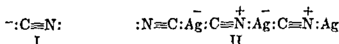
$$N_2 + 4\,C + Na_2CO_3 \longrightarrow 2\,NaCN + CO$$

In the Castner process sodamide at 500 to 600° reacts with carbon to form sodium cyanamide, and this at 800° reacts with more carbon to form sodium cyanide.



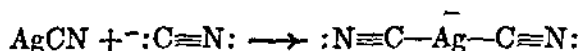
$$2\,Na + 2\,NH_3 \longrightarrow 2\,NaNH_2 + H_2$$
$$2\,NaNH_2 + C \longrightarrow Na_2(NCN) + 2\,H_2$$
$$\underset{\text{sodium cyanamide}}{Na_2(NCN)} + C \longrightarrow \underset{\text{sodium cyanide}}{2\,NaCN}$$

Sodium cyanide is an ionic compound composed of positive sodium and negative cyanide ions. In cyanide ion, carbon and nitrogen are joined by a triple bond, and each atom carries an unshared electron pair, I. Here the carbon atom carries a formal negative charge.



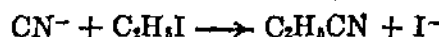
$$\underset{\text{I}}{^{-}{:}C{\equiv}N{:}} \qquad \underset{\text{II}}{{:}N{\equiv}C{:}\overset{-}{Ag}{:}C{\equiv}\overset{+}{N}{:}\overset{-}{Ag}{:}C{\equiv}\overset{+}{N}{:}Ag}$$

Silver cyanide is an insoluble solid in which the silver atom is believed to have a coordination number of two. It may coordinate with either the carbon or nitrogen atom, and thus form a long chain, part of which is shown as II. The bond to carbon is believed to be stronger than the one to nitrogen. Silver cyanide dissolves readily in a solution containing cyanide ions, owing to the formation of stable argenticyanide ion, in which silver has a coordination number of two.



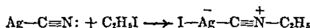
$$AgCN + {}^{-}{:}C{\equiv}N{:} \longrightarrow {:}N{\equiv}C{-}\overset{-}{Ag}{-}C{\equiv}N{:}$$

Sodium (or potassium) cyanide yields mainly an alkyl cyanide (some isocyanide) with an alkylating agent.



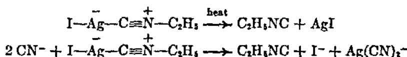
$$CN^- + C_2H_5I \longrightarrow C_2H_5CN + I^-$$

Silver cyanide yields mainly an isocyanide (some cyanide) with an alkylating agent. There is first formed an intermediate compound (structure below is uncertain).



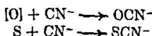
$$Ag{-}C{\equiv}N{:} + C_2H_5I \longrightarrow I{-}\overset{-}{Ag}{-}C{\equiv}\overset{+}{N}{-}C_2H_5$$

The intermediate is decomposed by heating or by the addition of a solution containing cyanide ions.



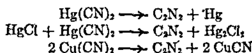
$$I{-}\overset{-}{Ag}{-}C{\equiv}\overset{+}{N}{-}C_2H_5 \xrightarrow{\text{heat}} C_2H_5NC + AgI$$
$$2\,CN^- + I{-}\overset{-}{Ag}{-}C{\equiv}\overset{+}{N}{-}C_2H_5 \longrightarrow C_2H_5NC + I^- + Ag(CN)_2^-$$

Potassium cyanide is changed to potassium cyanate by the action of an oxidizing agent and to potassium thiocyanate when heated with sulfur.



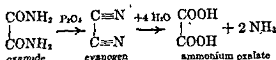
The structure of hydrogen cyanide has been a matter of dispute in the past, before the development of the Lewis theory of the chemical bond. At one time the bivalent carbon structure of Nef, H—N=C, was accepted by many, but now the nitrile structure, H—C≡N, is generally accepted. This topic is expanded further, following Structures.

Cyanogen, Oxalonitrile, N≡C—C≡N. This was discovered in 1815 by Gay-Lussac, who believed that he had succeeded in isolating the cyanide radical, which he had shown to be present in a number of compounds. Cyanogen can be prepared by heating mercuric cyanide, preferably in the presence of mercuric chloride; or it may be more conveniently prepared from aqueous copper sulfate and aqueous sodium cyanide, for the resulting cupric cyanide on heating decomposes to cuprous cyanide and cyanogen.



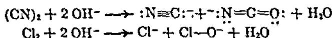
Cyanogen is a colorless, poisonous gas with a peculiar odor. It burns with a bluish flame. Its molecular weight in the gaseous state is 52, which corresponds to C_2N_2.

Its relationship to oxalic acid as oxalonitrile is shown by its formation from oxamide by heating with phosphorus pentoxide, and by the formation of ammonium oxalate when cyanogen stands for some time with water.



Other products also are formed, *viz.*, hydrocyanic acid, ammonium carbonate, urea, and azulmic acid.

Cyanogen resembles the halogens in its reaction with aqueous base, undergoing intramolecular oxidation and reduction. The products are cyanide and cyanate.



Structures. In Table 73 are listed data on interatomic distances and dipole moments of some organic cyanogen compounds. The carbon-to-nitrogen distances are essentially equivalent. The value of 1.16 Å is 79 per cent of the normal single-bond distance of 1.47 Å (Table 5, p. 14). This is the usual relationship between single and triple bonds. It is logical, therefore, to believe that a triple bond is present in the molecule of each substance. The

cyanide and isocyanide radicals —C≡N and —N⇶C, respectively, are among the most strongly dipolar groups known (Table 15, p. 33). The moment of the cyanide group is 3.14 *D* (3.34 *D*, of methyl cyanide, less 0.2 *D*, due to the ethyl group). The moment of the isocyanide group is 2.47 *D* (3.47 *D*, of ethyl isocyanide, less 1.0 *D*, the moment of the C—N bond).

TABLE 73 | **Data of Some Cyanogen Compounds**

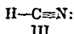
NAME	FORMULA	INTERATOMIC DISTANCE, Å		ELECTRIC DIPOLE MOMENT D
		C—N	C—C	
Hydrogen cyanide	H—C≡N:	1.16		2.6
Cyanide ion [a]	:C≡N: (with − charge)	1.15		
Cyanogen	:N≡C—C≡N:	1.16	1.37	0 3
Methyl cyanide	H_3C—C≡N:	1.16	1.49	3 34
Methyl isocyanide [a]	$H_3C—\overset{+}{N}≡\overset{-}{C}$:	1.18	1.44 [b]	3.47[c]

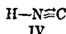
[a] A more convenient formula is H_3C—N⇶C, which means the nitrogen atom has contributed two electrons to form the bond indicated by the arrow (p. 13).
[b] This is the C—N distance; normal C—N distance is 1.47 Å, C=N, 1.27 Å.
[c] Value for ethyl isocyanide.

The molecule of cyanogen is essentially linear, otherwise its moment would be larger. The moments of the two cyano groups oppose each other and thus largely cancel out.

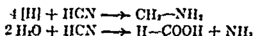
Other resonance forms are possible. For example, the value of 1.37 Å for the carbon-to-carbon distance in cyanogen is 0.17 Å less than the normal single-bond value of 1.54 Å and close to the double-bond value of 1.33 Å. This indicates considerable double-bond character, which is believed to arise from the contribution of other forms.

Hydrogen Cyanide. There are two possible structures for this compound, *viz.*, the nitrile (cyanide) structure, III, and the isocyanide (isonitrile) structure, IV.


H—C≡N:
III


H—N⇶C
IV

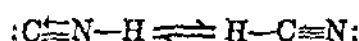
No decision can be made on the basis of bond distances (Table 73) or of chemical reactions. For example, hydrogen cyanide on reduction yields methylamine. Nitriles yield a primary amine and isocyanides yield an amine containing a methyl group (p. 391). On hydrolysis, hydrogen cyanide yields formic acid and ammonia. Nitriles yield ammonia and a carboxylic acid; isocyanides yield formic acid and an amine (p. 391).


$$4\,[H] + HCN \longrightarrow CH_3{-}NH_2$$
$$2\,H_2O + HCN \longrightarrow H{-}COOH + NH_3$$

However, hydrogen cyanide, like nitriles, undergoes both acid-catalyzed and base-catalyzed hydrolysis, while isocyanides undergo only acid hydrolysis.

On the basis of stability the nitrile structure is preferred. Isocyanides on heating rearrange to nitriles (p. 394). A carbon-to-hydrogen bond is more stable than a nitrogen-to-hydrogen bond by 30 kcal. Thus if the two carbon-to-nitrogen triple bonds have comparable stabilities, the nitrile structure is more stable by 30 kcal. On the basis of absorption spectra of hydrogen cyanide, more especially of the infrared spectra, there is no spectroscopic evidence for the existence of hydrogen isocyanide.

The two forms can be considered to be tautomeric forms, and thus to be in equilibrium.



The equilibrium lies very far to the right, for in this case ΔF and ΔH are not greatly different from each other (p. 24).

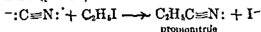
Alkyl Cyanides, Nitriles, R—C≡N:, and Alkyl Isocyanides, Carbylamines, R—N⃛C:. The former are named like alkyl halides, or preferably, as the nitriles of the acids to which they are converted on hydrolysis; the latter are named as alkyl isocyanides. Thus CH_3—C≡N: is methyl cyanide, or preferably acetonitrile, and CH_3—N≡C: is methyl isocyanide (sometimes methylcarbylamine or isoacetonitrile).

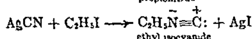
TABLE 74 | Constants of Some Normal Nitriles

NAME	FORMULA	M.P. °C	B.P. °C	SOLY. IN H_2O G./100 G.	DIEL. CONST.	DIPOLE MOMENT D
Formonitrile	H—CN	−13.4	25.7	misc.	115	2.6
Acetonitrile	CH_3—CN	−42	81.6	misc.	37	3.4
Propionitrile	C_2H_5—CN	−91.8	97.1	misc.	27	3.4
Butyronitrile	C_3H_7—CN	−111.9	117.6	3.1[a]	20	3.5
Valeronitrile	C_4H_9—CN	−96	140.7	0.98[a]	17	
Capronitrile	C_5H_{11}—CN	−79	163.9	0.32[a]		

[a] In 1 N KNO_3, g./100 g. solution.

Preparation. 1. *By the action of alkylating agents on metallic cyanides.* Alkali and alkaline earth cyanides yield mainly nitriles, silver cyanide yields mainly carbylamines (p. 385).





Reaction of sodium cyanide with an alkyl halide usually is carried out in aqueous alcohol. In the case of chlorides the reaction is so slow that sometimes

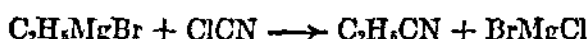
heating for days is necessary. Alkyl sulfates are more reactive. In fact, the *first nitrile was prepared (Pelouze, 1834) by heating potassium cyanide and* barium ethyl sulfate.



$$2\,KCN + Ba(OSO_2OC_2H_5)_2 \longrightarrow 2\,C_2H_5CN + BaSO_4 + K_2SO_4$$

The **nitrile synthesis** is an important method of lengthening the carbon chain, mainly because the starting materials are easily available. Since a nitrile can be converted to the corresponding primary alcohol through the intermediate amine, chain building can be accomplished step by step. Historically the nitrile synthesis was the first important method of building up the carbon chain. Now it is largely replaced by other synthetic methods, especially the Grignard synthesis (p. 138).

2. *Nitriles, by the action of Grignard reagents with cyanogen chloride.*



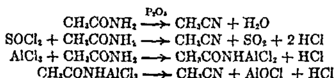
$$C_2H_5MgBr + ClCN \longrightarrow C_2H_5CN + BrMgCl$$

3. *Isocyanides, by the carbylamine reaction* (p. 358).



$$3\,NaOH + C_2H_5NH_2 + CHCl_3 \longrightarrow C_2H_5N{\equiv}C{:} + 3\,NaCl + 3\,H_2O$$

4. *Nitriles, by dehydration of amides, or ammonolysis of acids.* Calculation from bond and resonance energies shows that ΔH for the gas phase dehydration of an amide is +19 kcal. Thus a powerful dehydrating agent is needed at ordinary temperatures. For a laboratory preparation, heating with phosphorus pentoxide or, more conveniently, thionyl chloride or anhydrous aluminum chloride is satisfactory.



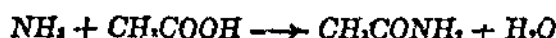
$$CH_3CONH_2 \xrightarrow{P_2O_5} CH_3CN + H_2O$$
$$SOCl_2 + CH_3CONH_2 \longrightarrow CH_3CN + SO_2 + 2\,HCl$$
$$AlCl_3 + CH_3CONH_2 \longrightarrow CH_3CONHAlCl_2 + HCl$$
$$CH_3CONHAlCl_2 \longrightarrow CH_3CN + AlOCl + HCl$$

In industry, fatty acids are available from fats. They can be converted directly to nitriles by passage with ammonia over a dehydrating catalyst, for example, thoria or silica gel at 500°



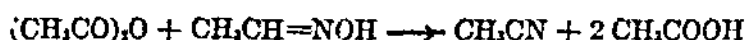
$$NH_3 + CH_3COOH \longrightarrow CH_3CN + 2\,H_2O$$

At lower temperatures the intermediate compounds, the amides, are formed.



$$NH_3 + CH_3COOH \longrightarrow CH_3CONH_2 + H_2O$$

5. *Nitriles, by dehydration of aldoximes.* These when heated with an acid chloride or anhydride usually are converted to nitriles.



$$(CH_3CO)_2O + CH_3CH{=}NOH \longrightarrow CH_3CN + 2\,CH_3COOH$$

Since ΔH for the gas phase dehydration of an oxime (from bond energies) is −45 kcal., a mild dehydrating agent is sufficient.

Physical Properties. Nitriles and isocyanides are colorless liquids. The former have pungent odors, the latter as usually prepared have powerful, disgusting odors;

the former are neutral liquids of not marked physiological properties; the latter are weak bases (carbylamines) and are highly poisonous. The formation of an isocyanide often serves as a test for a primary amine, owing to the powerful odor of the product. Nitriles distil without decomposition; lower isocyanides when heated quickly may decompose explosively; heated more slowly they may polymerize, and the polymer, at higher temperatures, may decompose to yield the corresponding nitrile. Some physical constants of lower derivatives are listed in Table 75.

TABLE 75 | Constants of Some Cyanogen Compounds

NAME	FORMULA	M.P. °C	B.P. °C	ΔHc, KCAL./MOLE	
				C_v	C_p
Cyanogen	N≡C—C≡N	−27.9	−21.3		−259.6 [a]
Hydrogen cyanide	H—C≡N	−13.4	25.7		−158.6 [a]
Methyl cyanide	CH_3—C≡N	−42	81.6	−302.5	−302.6 [b]
Ethyl cyanide	C_2H_5—C≡N	−91.8	97.1	−456.2	−456.6
n-Propyl cyanide	C_3H_7—C≡N	−111.9	117.6	−613.1	−613.7
Methyl isocyanide	CH_3—N⇄C	−45	59.6	−317.2	−317.4
Ethyl isocyanide	C_2H_5—N⇄C	−66	78.1	−477.0	−477.4
n-Propyl isocyanide	C_3H_7—N⇄C		98		−638.6
Methyl isocyanate	CH_3—N=C=O		37.8	−268.9	−269.3
Ethyl isocyanate	C_2H_5—N=C=O		60	−424.2	−424.4
Methyl thiocyanate	CH_3—S—C≡N	−54.5	131	−452.1	−453.1
Ethyl thiocyanate	C_2H_5—S—C≡N	−85.5	144.4	−612.5	−613.8
Methyl isothiocyanate	CH_3—N=C=S	35.9	117.5	−441.6	−442.6
Ethyl isothiocyanate	C_2H_5—N=C=S	−5.9	132	−602.8	−604.1

[a] In the gaseous state. [b] In the liquid state; ΔHc in the gaseous state, −312.1 kcal.

Reactivity. Nitriles are relatively inert but undergo a number of reactions under acidic or basic catalysis. Isocyanides are more reactive.

The complete structure of acetonitrile involves a dipolar form VI in addition to the covalent form V.



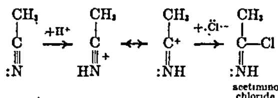
Although VI has a lower stability than V because the carbon atom of VI has only a sextet of electrons, the charge distribution is favorable to stability. Thus the carbon atom of acetonitrile and of other nitriles, like the carbon atom of aldehydes and ketones, is electrophilic, and would be expected to form a bond with a nucleophilic reagent. However, since nitrogen is not as electronegative as oxygen, a nitrile is less reactive than an aldehyde.

Although nitriles are neutral substances, under anhydrous conditions they react with acids to form addition compounds. The first step in this process is the attach-

ment of a proton to the unshared electron pair. The resulting conjugate acid (nitrilium ion) is a resonance hybrid of two forms, VII and VIII.



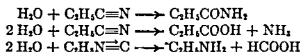
The contribution of VIII to the structure of the nitrilium ion would be expected to be more important than the contribution of VI to the structure of the nitrile. Thus reaction with a nucleophilic reagent, for example, chloride ion, takes place more readily than in the absence of an acid.



Similar mechanisms can be assumed in other acid-catalyzed reactions of nitriles, for example, those with water and with alcohols. Here, however, the reactant is a neutral molecule, rather than a negative ion. It reacts by virtue of an unshared electron pair on an oxygen atom.

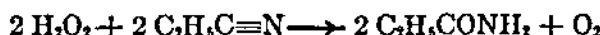
Reactions. Those of nitriles are the more important. Usually, as in hydrolysis, heating is necessary and except with very reactive carbanions, acidic or basic catalysis is necessary.

1. *Hydrolysis.* This is the most important reaction. Nitrile hydrolysis is catalyzed by either hydronium or hydroxide ion. Isocyanide hydrolysis is not affected by hydroxide ion but is so greatly accelerated by hydronium ion that the reaction may proceed explosively. A nitrile is converted, through the amide, to ammonia and the corresponding carboxylic acid, an isocyanide to formic acid and a primary amine.



$$H_2O + C_2H_5C{\equiv}N \longrightarrow C_2H_5CONH_2$$
$$2\,H_2O + C_2H_5C{\equiv}N \longrightarrow C_2H_5COOH + NH_3$$
$$2\,H_2O + C_2H_5N{\overrightarrow{=}}C \longrightarrow C_2H_5NH_2 + HCOOH$$

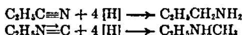
Usually an amide cannot be isolated in good yield when a nitrile is being hydrolyzed under acidic or basic conditions, because simple aliphatic amides react more rapidly than the corresponding nitriles. However, in dilute aqueous base at about 40°, hydrogen peroxide converts many nitriles to amides by a reaction which proceeds more slowly at the next step.



$$2\,H_2O_2 + 2\,C_2H_5C{\equiv}N \longrightarrow 2\,C_2H_5CONH_2 + O_2$$

Amides often are prepared this way.

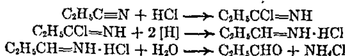
2. *Reduction.* Both types can be reduced by means of hydrogen over nickel at 180°; nitriles are also conveniently reduced by metallic sodium in boiling alcohol. Nitriles yield primary amines, isocyanides secondary methylamines.



$$C_2H_5C{\equiv}N + 4\,[H] \longrightarrow C_2H_5CH_2NH_2$$
$$C_2H_5N{\overrightarrow{=}}C + 4\,[H] \longrightarrow C_2H_5NHCH_3$$

Side reactions lead to formation of other products, as di- and tri-*n*-propylami propionitrile.

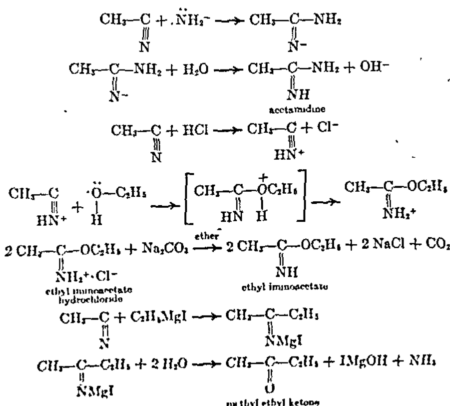
Aldehydes can be obtained from nitriles when the reduction is effected by anhydrous stannous chloride and hydrogen chloride in absolute ether.



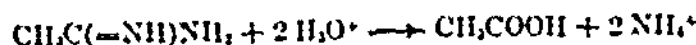
First, hydrogen chloride adds; the resulting propionimido chloride is reduced, yielding *propionaldimine hydrochloride*, which separates in the form of an addition compound with stannic chloride as $(C_2H_5CH{=}NH_2Cl)_2 \cdot SnCl_4$. On the addition of water the aldimine readily hydrolyzes to the aldehyde, another example of the hydrolytic scission of the C=N bond (see Oximes and Hydrazones, p. 271).

Lithium aluminum hydride reduces nitriles easily. At room temperature the product is a primary amine, at Dry Ice temperature aldehyde can be the principal product, provided the reducing agent is added slowly to the nitrile.

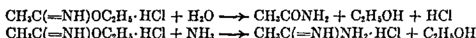
3 Addition. Many reagents add to nitriles and isocyanides. Three important reactions of nitriles are those with ammonia, alcohols, and Grignard reagents, yielding respectively, amidines, iminoesters, and ketones.



Amidines, of which acetamidine is an example, are formed more readily with potassium amide than with ammonia. The potassium salt of the amidine is decomposed rapidly by water, since amidines are very weak acids. Actually they are strong monoacid bases. They are readily hydrolyzed when heated in dilute acid.

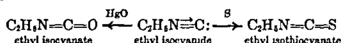


Imino esters, of which ethyl iminoacetate is an example, are often called imino ethers, and are so named, for example, acetimino ethyl ether. With water the hydrochloride is rapidly decomposed to acetamide, and with somewhat more than one equivalent of ammonia in alcoholic solution is slowly converted into acetamidine hydrochloride.



The formation of ketones by the action of Grignard reagents on nitriles is a general method for their preparation (p. 258).

Isocyanides are oxidized easily to isocyanates, and add sulfur above 100° to form isothiocyanates.

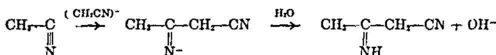


4. *Condensation.* In the presence of metallic sodium two molecules of nitrile condense with each other. The first step is the formation of a sodium salt, owing to the activating effect of the cyano group on an α-hydrogen atom. Part of the nitrile is cleaved to methane and sodium cyanide.

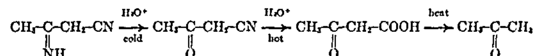


In place of metallic sodium, which destroys part of the material, a very strong base is preferred, for example, lithium diethylamide, $LiN(C_2H_5)_2$. Sodium ethoxide and sodamide often are used, but sometimes are less satisfactory. Since the nitrile is only an extremely weak acid, the base must be very strong.

Reaction is believed to involve one molecule of negative ion and one of nitrile. The resulting ion yields the cyanoimine on addition of water

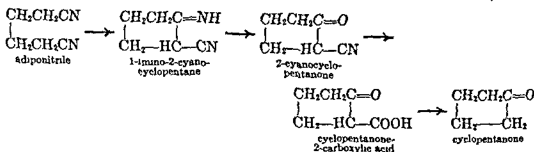


The cyanoimine hydrolyzes readily in cold aqueous acid to a cyanoketone.



The cyanoketone when heated is hydrolyzed to acetoacetic acid, which like other β-keto acids, decarboxylates when heated (p. 321). Thus in two operations the following steps are carried out: acetonitrile ⟶ cyanoacetoneimine ⟶ cyanoacetone ⟶ β-ketobutyric acid ⟶ acetone.

This synthetic method is especially valuable in the synthesis of cyclic ketones. An α,ω-dicyanide condenses with itself. Thus adiponitrile with a trace of sodium ethoxide in alcoholic solution gives a quantitative yield of 1-imino-2-cyanocyclopentane. When heated with aqueous acid this is converted to the cyclic ketone, cyclopentanone, through the two hydrolysis steps and the decarboxylation step similar to the ones above.

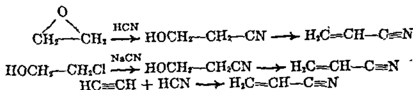


Ketones having large rings can be prepared by the **high dilution** technique of Ziegler, who runs the dicyanide slowly into a solvent containing some of the condensing agent, in this case lithium diethylamide. The reaction between two molecules is kept to a minimum because of the low concentration. Cycloheptadecanone, having a ring of seventeen carbon atoms, has been obtained in about 50 per cent yield.

5. *Rearrangement.* Isocyanides when heated for some time (250–300°) rearrange to nitriles. This indicates that nitriles are more stable than isocyanides. This conclusion is substantiated by the heats of combustion data shown in Table 74. The values for isocyanides are much higher than those for isomeric nitriles (*ca.* 15 kcal.).

Dinitriles. The main interest in these compounds, aside from their conversion to large ring ketones, lies in their conversion through reduction to diamines, which are important in the manufacture of long chain polyamides (p. 381). The most important dinitrile is adiponitrile. It may be obtained from adipic acid by the usual steps or from 1,4-dichlorobutane (see Tetrahydrofuran, Chap. 44).

Unsaturated Nitriles. Acrylonitrile (vinyl cyanide), $CH_2{=}CH{-}C{\equiv}N$, is the most important of these. It can be obtained from ethylene oxide, ethylene chlorohydrin, or acetylene.



Acrylonitrile is an important industrial product. By copolymerization with butadiene it is converted into synthetic rubber, Buna N (p. 92). It yields a polymeric acrylonitrile from which a useful fiber is made ("Orlon").

Cyanic Acid, $H{-}N{=}C{=}O$ or $H{-}O{-}C{\equiv}N$. Although salts are stable, for example, potassium cyanate, the acid is quite unstable (because of polymerization) and also is very reactive. Salts of cyanic acid are obtained by oxidation of cyanides (p. 386).

The free acid can be prepared by heating cyanuric acid, $C_3H_3O_3N_3$, a trimer of cyanic acid, in a stream of carbon dioxide.

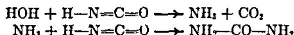


$$C_3H_3O_3N_3 \longrightarrow 3\ HNCO$$

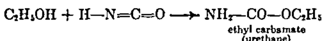
On cooling the gas to below 0°, cyanic acid condenses as a liquid ($K_a = 1.5 \times 10^{-4}$). Even at 0° it polymerizes rapidly. The product is mainly a white, amorphous powder, cyamelide, which probably is a linear polymer. At a higher temperature and in the gas phase some cyanuric acid, the cyclic trimer (p. 398), is formed, as well as cyamelide. The proportion of trimer is greater the higher the temperature of polymerization.

Only one cyanic acid is known, although two structures are possible. From the infrared absorption spectra it has been found that gaseous cyanic acid is almost entirely the isomer having the imine structure. The two forms of cyanic probably are in tautomeric equilibrium, like the two forms of hydrogen cyanide. Two series of esters are known, *viz.*, the cyanates, R—O—C≡N, and the isocyanates, R—N=C=O. Cyanates polymerize rapidly to esters of cyanuric acid. Isocyanates are stable compounds (see below).

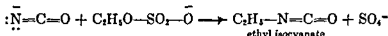
Cyanic acid undergoes rapid hydrolysis to ammonia and carbonic acid, with formation of some urea, which results from a reaction of ammonia with some of the cyanic acid.



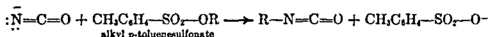
The acid also reacts rapidly with alcohols, with formation of esters of carbamic acid (urethanes) as the main products.



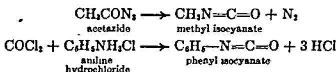
Isocyanates. The method first used for their preparation, *viz.*, heating potassium cyanate with an alkyl potassium sulfate (Wurtz, 1854) gives small yields, for much cyanurate (from polymerization of cyanate) is formed.



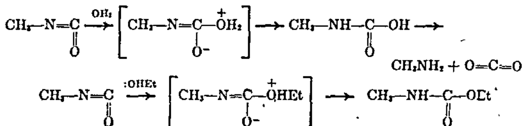
Better yields result from heating potassium cyanate with dialkyl sulfates or with alkyl sulfonates.

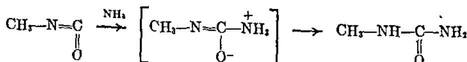


Convenient methods of preparation are the decomposition of azides (p 375) and the action of phosgene on amines (usually salts of amines).

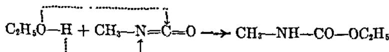


Isocyanates hydrolyze readily in acidic or basic solution. Also they react rapidly with ammonia or with amines, readily with alcohols. The carbon atom of an isocyanate is more electrophilic than that of a nitrile or an aldehyde since it is in combination with two electronegative atoms. The uncatalyzed reactions with water, alcohol, and ammonia are pictured as proceeding via similar mechanisms.





The products are similar, except that N-methylcarbamic acid, formed as an intermediate in the hydrolysis reaction, is unstable and undergoes decarboxylation to methylamine. Alcohol is converted to ethyl N-methylcarbamate (methylurethane) and ammonia to methylurea. Methylamine yields symmetrical dimethylurea. The hydrolysis reaction is one step in the Hofmann degradation of an amide. Sometimes the reactions are written as addition to a double bond, as in the case of alcohol.

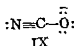
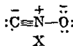
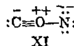


The identification of an alcohol or amine often is aided by reaction with an isocyanate, since many N-substituted carbamates and disubstituted ureas are solid, especially when prepared from an aromatic isocyanate, for example, phenyl isocyanate, $C_6H_5—N=C=O$. An isocyanate often contains the corresponding disubstituted urea as an impurity, because partial hydrolysis gives the amine, and this then reacts with more isocyanate.

Fulminic Acid, H—O—N⇄C:. Mercuric fulminate is obtained from mercuric nitrate, ethyl alcohol, and excess nitric acid. It is a powerful explosive and is sensitive to shock. It is much used in percussion caps or in other detonators for initiating the decomposition of other explosives. Silver fulminate may be obtained in a similar manner. Sodium fulminate, in aqueous solution, is obtained by the action of sodium amalgam on mercuric fulminate under water. Acidification of this solution, cold, liberates fulminic acid, which can exist in solution (water or ether) or in the vapor phase. It polymerizes rapidly in solution. The acid and salts are highly poisonous.

Silver fulminate, AgONC, is isomeric with silver cyanate, AgNCO. The word, isomerism, was first used in connection with these two compounds, about 1825, by Berzelius.

Isomerism of Cyanates and Fulminates. For the uninegative ions composed of one atom each of carbon, oxygen, and nitrogen there are three isomeric structures theoretically possible, depending upon which atom is the middle atom. These can be represented by IX, X, and XI, respectively, although other resonance forms are possible.

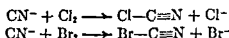




The order of stability of these ions, predicted on the basis of formal charges, would be expected to be IX > X > XI. Of salts composed of any of these ions the most stable actually are the cyanates, as for example, potassium cyanate. These have structure IX. Less stable are the fulminates, X. Metallic compounds having structure XI are not known.

The order of stability of organic compounds having the above grouping of atoms is: isocyanates, $R—N=C=O$ > cyanates, $R—O—C\equiv N$ > nitrile oxides, $R—C\equiv N \rightarrow O$. It is noted that for each pair of organic compounds derived from IX or X by attachment of an organic radical, the more stable isomer is the one in which R is attached to the less electronegative element. Isocyanates are stable compounds, but cyanates

polymerize rapidly to cyanurates. Although alkyl nitrile oxides are not known, when R is an aromatic radical the compound is stable. On the other hand, organic fulminates, R—O—N⇄C, are not known. Derivatives of the hypothetical acid, H[CON] are not known.

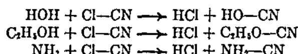
Cyanogen Halides. Cyanogen chloride and bromide may be prepared by the action of the respective halogen on sodium or potassium cyanide in aqueous solution.



$$CN^- + Cl_2 \longrightarrow Cl{-}C{\equiv}N + Cl^-$$
$$CN^- + Br_2 \longrightarrow Br{-}C{\equiv}N + Br^-$$

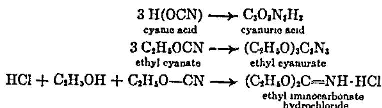
Cyanogen bromide may be conveniently prepared from potassium (or sodium) cyanide, bromide, and bromate by adding dilute sulfuric acid. These cyanogen halides are toxic substances and were used to some extent as poison gases in World War I. The chloride melts at −6° and boils at 13.8°; the bromide, 52° and 61.6°. On standing each polymerizes, the chloride to **cyanuric chloride,** $C_3N_3Cl_3$, the bromide to **cyanuric bromide,** $C_3N_3Br_3$ (p. 398).

Cyanogen chloride and bromide are essentially acyl halides of cyanic acid, for they react with water to form the acid, with alcohols to form cyanates, and with ammonia to form cyanamide.



$$HOH + Cl{-}CN \longrightarrow HCl + HO{-}CN$$
$$C_2H_5OH + Cl{-}CN \longrightarrow HCl + C_2H_5O{-}CN$$
$$NH_3 + Cl{-}CN \longrightarrow HCl + NH_2{-}CN$$

However, because of the rapid polymerization of cyanic acid and ethyl cyanate, the actual product of the first reaction is a mixture of cyanuric acid and cyamelide and of the second reaction, ethyl cyanurate; also, ethyl cyanate reacts rapidly with ethyl alcohol, to form ethyl iminocarbonate.



$$\underset{\text{cyanic acid}}{3\,H(OCN)} \longrightarrow \underset{\text{cyanuric acid}}{C_3O_3N_3H_3}$$
$$\underset{\text{ethyl cyanate}}{3\,C_2H_5OCN} \longrightarrow \underset{\text{ethyl cyanurate}}{(C_2H_5O)_3C_3N_3}$$
$$HCl + C_2H_5OH + C_2H_5O{-}CN \longrightarrow \underset{\text{ethyl iminocarbonate hydrochloride}}{(C_2H_5O)_2C{=}NH \cdot HCl}$$

Cyanamide, $NH_2C{\equiv}N$. This is the amide of cyanic acid, as shown by its formation and preparation from cyanogen bromide and ammonia.



$$2\,NH_3 + BrCN \longrightarrow NH_2CN + NH_4Br$$

Like acetamide it is both a weak acid and a weak base. Both hydrogen atoms are replaceable by metals.

Sodium cyanamide, Na_2NCN, is formed when sodamide and coke are heated to about 400°.



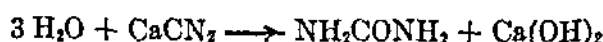
$$2\,NaNH_2 + C \longrightarrow Na_2NCN + 2\,H_2$$

Calcium cyanamide, $CaCN_2$, is formed in one important process of nitrogen fixation. Nitrogen is passed over finely ground calcium carbide. The reaction is started by heating one spot to about 1000°, for the heat of reaction is sufficient to maintain the mass at the desired temperature.



$$CaC_2 + N_2 \longrightarrow CaCN_2 + C \quad \Delta H = -98\ \text{kcal.}$$

This crude calcium cyanamide contains unreacted calcium carbide, which is decomposed by adding the correct amount of water. In this form it is used as a *fertilizer.* Partial hydrolysis yields urea, while hydrolysis with *steam yields ammonia.*



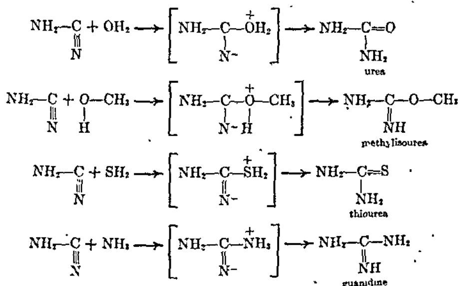
$$3\ H_2O + CaCN_2 \longrightarrow NH_2CONH_2 + Ca(OH)_2$$



$$4\ H_2O + CaCN_2 \longrightarrow 2\ NH_3 + CaCO_3$$

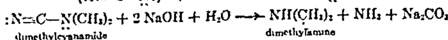
Cyanamide melts at 44° and boils at 140° (19 mm.). It is *very soluble in water, alcohol, or ether.* It can be obtained from either the sodium or calcium salt with sulfuric acid by careful manipulation. From the sodium salt the acid used should have such a concentration that the water present is retained by the resulting sodium sulfate as the decahydrate. Cyanamide is then extracted by alcohol or ether.

Cyanamide resembles other nitriles in undergoing many addition reactions.

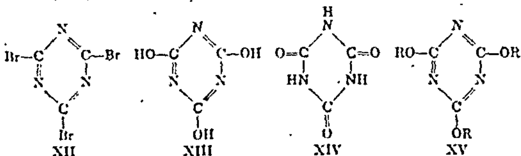


The reaction with water is catalyzed by hydronium or hydroxide ion; the one with alcohol is carried out in the presence of a strong acid. Secondary amines can be prepared by the action of an alkylating agent on sodium cyanamide, followed by hydrolysis.





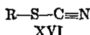
Cyanuric Acid, $C_3O_3N_3H_3$. This is best obtained by the hydrolysis of cyanuric bromide, XII, the trimer of cyanogen bromide.

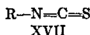


Two tautomeric forms of cyanuric acid are possible, *viz.*, the lactim (enol) form, XIII, and the lactam (keto) form, XIV. Only one cyanuric acid is known but there are derivatives of both forms. The alkyl cyanurates, which result from the rapid polymerization of alkyl cyanates, have structure XV.

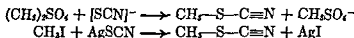
Thiocyanic Acid, H(NCS). This is a gas and is formed by the action of potassium bisulfate on potassium thiocyanate. The acid is not very stable in the gaseous state, and is quite unstable as the solid, which is obtained by cooling the gas to −30°. Solid, yellowish products result from the polymerizations.

Two series of esters are known, the thiocyanates, XVI, and the isothiocyanates, XVII.

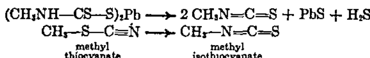




Alkyl thiocyanates are obtained by the action of alkylating agents on potassium or silver thiocyanate. Methyl thiocyanate results from dimethyl sulfate and potassium thiocyanate (saturated aqueous solution) or methyl iodide and silver thiocyanate.



Isothiocyanates are formed by heating the lead or mercury salts of N-alkyldithiocarbamic acid (p. 359). Also, they are slowly formed from thiocyanates when these are heated sufficiently (150–200°), or merely when in contact with cadmium iodide at 20°.

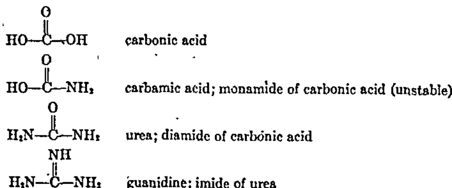


The thiocyanates are liquids having disagreeable, garliclike odors, the isothiocyanates, mustardlike odors. Allyl isothiocyanate is an important ingredient of oil of mustard. The rearrangement of thiocyanates shows that isothiocyanates are more stable than thiocyanates. It is evident from Table 74 that thiocyanates have higher heats of combustion than do isomeric isothiocyanates, the difference being about 10 kcal.

Isothiocyanates are sometimes used in the identification of alcohols or amines, undergoing reactions similar to those of isocyanates (p. 395).

COMPOUNDS RELATED TO CARBONIC ACID

At various times different derivatives of carbonic acid have been described. It is worth while pointing out the relationships among them:



$H_2N—C(=O)—OC_2H_5$	urethane; ester of carbamic acid
$H—O—C≡N$	cyanic acid; nitrile of carbonic acid (unstable)
$H—N=C=O$	isocyanic acid; imide of carbonic acid (unstable)
$H_2N—C≡N$	cyanamide; nitrile of carbamic acid; amide of cyanic acid
$Cl—C≡N$	cyanogen chloride; acid chloride of cyanic acid
$Cl—C(=O)—Cl$	phosgene or carbonyl chloride; acid chloride of carbonic acid
$Cl—C(=O)—OC_2H_5$	ethyl chlorocarbonate or chloroformate; mixed ester and acid chloride of carbonic acid

All of these compounds when heated with an aqueous strong acid yield carbon dioxide, or with aqueous strong base, a carbonate. Those having nitrogen yield also an ammonium salt with an acid or ammonia with a base.

PROBLEMS

1. For the following write the more important resonance forms (those of comparable stability) and then the less important ones.

a) methyl cyanide
b) methyl isocyanide
c) cyanogen
d) acetimino chloride
e) acetamidine
f) methyl iminoacetate
g) cyanate ion
h) methyl cyanate
i) methyl isocyanate
j) methyl carbonate
k) fulminate ion
l) chlorocyanogen
m) bromocyanogen
n) cyanamide
o) methyl thiocyanate
p) methyl isothiocyanate
q) urea
r) methylisourea
s) thiourea
t) guanidine

2. Starting with sodium cyanide as the only nitrogen compound, show how to prepare:

a) isocapronitrile
b) 1-cyano-2-ethylbutane
c) *n*-valeramide
d) *n*-hexanoamide
e) ethyl isocyanide
f) *n*-amyl isocyanide
g) methylethylamine
h) methyl-*n*-amylamine
i) methyl isocyanate
j) *n*-amyl isocyanate
k) methyl isothiocyanate
l) *n*-amyl isothiocyanate
m) methyl cyanurate
n) *n*-amyl cyanurate
o) lactonitrile
p) oxalonitrile
q) succinonitrile
r) adiponitrile
s) succinimide
t) *n*-butyl iminoacetate

3. Write equations for reactions involved in preparing the following, starting with *n*-propyl alcohol and sodium cyanide or sodium cyanamide as the only carbon compounds and with ammonia as the only other nitrogen compound.

a) propionitrile
b) acetonitrile
c) *n*-butyronitrile
d) *n*-valeronitrile

e) α-hydroxy-*n*-butyronitrile
f) α-hydroxy-α-ethyl-*n*-butyronitrile
g) *n*-propyl isocyanide
h) *n*-butylamine
i) *n*-butyl isocyanide
j) *n*-amylamine
k) methyl-*n*-propylamine
l) methyl-*n*-butylamine
m) *n*-propyl isothiocyanate
n) *n*-butyl isothiocyanate
o) propionamidine
p) *n*-butyramide
q) *n*-butyramidine
r) *n*-propyl iminopropionate
s) *n*-propyl imino-*n*-butyrate
t) *n*-propyl N-ethylcarbamate
u) di-*n*-propylamine
v) *n*-propylcyanamide
w) *n*-propylurea
x) *n*-propylisourea
y) *n*-propylisothiourea
z) *n*-propylguanidine

4. Show how to obtain the following, having available *n*-butyl alcohol as the only carbon compound and any nitrogen compound except hydrogen cyanide and/or its inorganic derivatives.

a) *n*-butyronitrile
b) *n*-butyrazide
c) propionitrile
d) *n*-butyramide
e) *n*-butyramidine
f) *n*-butyl imino-*n*-butyrate
g) *n*-propyl isocyanate
h) *n*-propylurea
i) *n*-butyl N-*n*-propylcarbamate
j) *n*-propyl N-*n*-propylcarbamate
k) isopropyl N-*n*-propylcarbamate
l) *sym*-di-*n*-propylurea
m) *sym*-*n*-propyl-*n*-butylurea
n) *n*-propyl imino *n*-butyrate
o) 3-cyano-4-heptanone
p) α-ethyl-β-ketohexanoic acid

5. Show the steps in a practical laboratory preparation of the following from compounds of fewer carbon atoms.

a) *n*-propyl carbamate
b) *n*-butyl carbamate
c) methyl N-ethylcarbamate
d) *n*-propyl N-methylcarbamate
e) methylcyanamide
f) ethylurea
g) ethylisourea
h) ethylthiourea
i) ethylisothiourea
j) methylguanidine
k) diethylcyanamide
l) di-*n*-propylcyanamide
m) *sym*-dimethylurea
n) *unsym*-dimethylurea
o) *sym*-methylethylurea
p) *unsym*-methylethylurea
q) N,N,N′-trimethylurea
r) N-methyl-N′N′-di-*n*-propylurea
s) N,N,N′-trimethylguanidine
t) N-methyl-N′,N′-di-*n*-propylguanidine

6. Write a balanced equation for the reaction when the following is heated with an excess of aqueous sodium hydroxide.

a) *sym*-dimethylurea
b) *unsym*-dimethylurea
c) diethylcyanamide
d) ethyl carbamate
e) ethylcyanamide
f) ethylguanidine
g) ethylisourea
h) ethyl N-methylcarbamate
i) *sym*-ethyl-*n*-propylurea
j) *unsym*-ethyl-*n*-propylurea
k) methyl carbamate
l) methyl cyanurate
m) methyl N-ethylcarbamate
n) methyl iminopropionate
o) methylisourea
p) propionamidine
q) propionitrile
r) *n*-propylguanidine
s) *n*-propyl isocyanate
t) *n*-propyl isothiocyanate

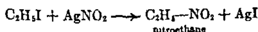
CHAPTER 24

Nitroparaffins

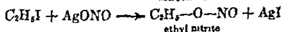
The nitroparaffins have become of increasing industrial importance since 1940, when they were first produced on a pilot plant scale by the vapor phase reaction between paraffin hydrocarbons and nitric acid at temperatures of 400 to 450°.

Preparation. The first reaction mentioned below was discovered by Victor Meyer in 1872; formerly it was the usual method of preparation and an important step in a procedure for distinguishing the three classes of alcohols

1. *Action of alkyl halides with silver nitrite.* Here the isomeric alkyl nitrites, the usual products with sodium and potassium nitrites, are also formed, the relative amounts varying with the alkyl halides and the experimental conditions.



$$C_2H_5I + AgNO_2 \longrightarrow \underset{\text{nitroethane}}{C_2H_5{-}NO_2} + AgI$$



$$C_2H_5I + AgONO \longrightarrow \underset{\text{ethyl nitrite}}{C_2H_5{-}O{-}NO} + AgI$$

It will be recalled that silver cyanide and sodium cyanide give different products with alkylating agents (p. 385).

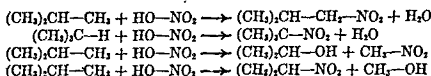
2. *Nitration of paraffins.* Reaction in the liquid phase is very slow and yields usually are poor, owing to the oxidizing action of nitric acid. The acid must be dilute. Yields have been as high as 60 per cent, as when *n*-hexane and nitric acid (sp. gr., 1.075) are heated in a sealed tube at 140°.



$$C_6H_{14} + HO{-}NO_2 \longrightarrow C_6H_{13}{-}NO_2 + H_2O$$

The reaction is fastest at tertiary carbon atoms, slowest at primary carbon atoms. The products are called primary, secondary, and tertiary nitroparaffins, depending on the type of carbon atom to which the nitro group is attached.

In the high temperature gas phase reaction, which is possible over the range 250 to 600°, nitration proceeds at all possible positions. Isobutane yields mainly 1-nitro-2-methylpropane and some 2-nitro-2-methylpropane. In addition, there are considerable amounts of nitromethane and 2-nitropropane arising from cleavage of a carbon-to-carbon bond with, it is believed, concurrent formation of an alcohol.



$$(CH_3)_2CH{-}CH_3 + HO{-}NO_2 \longrightarrow (CH_3)_2CH{-}CH_2{-}NO_2 + H_2O$$
$$(CH_3)_3C{-}H + HO{-}NO_2 \longrightarrow (CH_3)_3C{-}NO_2 + H_2O$$
$$(CH_3)_2CH{-}CH_3 + HO{-}NO_2 \longrightarrow (CH_3)_2CH{-}OH + CH_3{-}NO_2$$
$$(CH_3)_2CH{-}CH_3 + HO{-}NO_2 \longrightarrow (CH_3)_2CH{-}NO_2 + CH_3{-}OH$$

Only a small amount of alcohol is detected, however, owing to its oxidation by nitric acid. Other reaction products are acids, aldehydes, ketones, carbon monoxide, carbon dioxide, and nitric oxide.

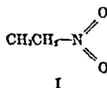
3. *Oxidation of amines.* Even under the best conditions primary amines give only very low yields of nitroparaffins when oxidized with peroxysulfuric acid. Ethylamine, for example, yields nitroethane, but acetic acid is the main product, with substantial amounts of acetonitrile and acetaldoxime.

TABLE 76 | Constants of Some Nitroparaffins

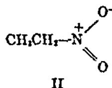
NAME	M.P. °C	B.P. °C	SP. GR. 20°/20°	SOLUBILITY, ML./100 ML.	
				RNO_2 in H_2O	H_2O in RNO_2
Nitromethane	−29	101.2	1.139	9.5	2.2
Nitroethane	−90	114	1.052	4.5	0.9
1-Nitropropane	−108	131.6	1.003	1.4	.5
2-Nitropropane	−93	120.3	0.992	1.7	.6
1-Nitrobutane		153	.975		
2-Nitrobutane		140	.968		

Properties of Nitroparaffins. In Table 76 are listed some nitroparaffins. In general, the lower members up to nitroundecane, $C_{11}H_{23}NO_2$, are liquids. They have rather large dipole moments (nitromethane, 3.5; nitroethane, 3.5) and dielectric constants (nitromethane, 39; nitroethane, 30), both rather large for organic compounds (however, see Amides, p. 371)

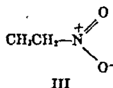
Structure of Nitroethane. Formerly, and sometimes even now, the structures of the nitroparaffins are written in terms of classical valence theory, for example, I. Such structures are not in conformity with the octet rule (p. 11) and therefore are incorrect. Nitroethane, for example, is II or III.



I



II

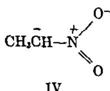
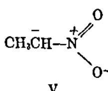
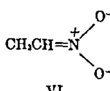
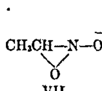


III

Actually it is a combination of II and III, owing to resonance involving these two electronic forms. The bond distances and bond angles of nitromethane listed in Table 8, page 20, are best explained on the basis of resonance.

The salts of nitromethane (see next heading) have more resonance forms, IV, V, and VI. The possibility of another form, VII, making any contribu-

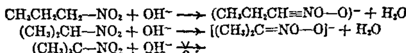
tion to the overall structure is quite remote, because this would necessitate a change in the relative positions of atoms in the molecule.

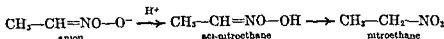
The contributions of IV and V to the overall structure are significant enough to impart a high degree of reactivity and permit condensation and other reactions to take place readily. When an acid is added to the salt, the proton appears to be attached first to a negatively charged oxygen atom and finally ends up on the carbon atom.

Reactions of Nitroparaffins. Of the numerous reactions, only some of the most important can be mentioned here.

1. *Acid properties.* Nitroparaffins having a hydrogen atom on the α-carbon atom have weakly acidic properties (K_a of nitromethane is 6×10^{-11}; of nitroethane is 3.5×10^{-9}), but those without an α-hydrogen atom are neutral. Primary and secondary nitroparaffins, for example, 1-nitro- and 2-nitropropane, dissolve in dilute aqueous sodium hydroxide, but tertiary do not, for example, 2-nitro-2-methylpropane.



When a strong acid is added to a cold solution of the salt, the nitroparaffin is not formed at once, but instead another acid, an isomer of the nitroparaffin, is formed. This changes over to the nitro compound.



The isomeric acid is more soluble in water than is the nitroparaffin and is a stronger acid. It is called an aci-nitroparaffin or sometimes a nitronic acid. The ionization constant of aci-nitroethane is 4×10^{-4}.

Nitroparaffins sometimes are called **pseudo acids** (false acids) because of the slowness with which they react with bases, whereas true acids react instantaneously with bases. On the other hand the aci-forms are true acids. They dissolve readily in water, react rapidly with bases and with bromine, and show conductance in aqueous solution. The nitroparaffins are much less soluble in water, react only slowly with bases and with bromine, and show very low conductance in aqueous solution. The salts also react rapidly with bromine

2. *Reduction.* Two types of reduction products are possible, hydroxylamines, R—NHOH, and primary amines, R—NH_2, as well as more complicated compounds, resulting from side reactions. With tin and aqueous hydrochloric acid, zinc dust and glacial acetic acid, or zinc dust and boiling

water, which does not carry the reduction further, nitromethane yields methylhydroxylamine.



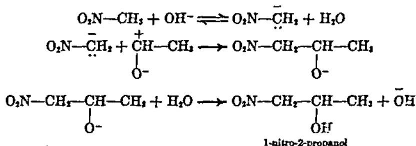
Catalytic hydrogenation may give the hydroxylamine or the amine. Numerous reducing agents yield the amine, for example, many metals (including tin) with acids, sodium amalgam with water, and sodium hydrosulfite. Iron and hydrochloric acid give good yields of the amine.



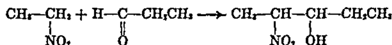
This result shows that in nitromethane the nitrogen atom is directly joined to the carbon atom, whereas the isomeric methyl nitrite yields methanol and ammonia on reduction.



3. *Condensation with aldehydes.* This reaction of primary and secondary, but not tertiary, nitroparaffins takes place in the presence of a base, for example, sodium (or potassium) hydroxide, carbonate, bicarbonate, or methoxide or calcium hydroxide. Other reactions also can take place, for example, *the aldol condensation, involving the aldehyde but not the nitroparaffin.* Nitromethane and acetaldehyde yield 1-nitro-2-propanol. It is convenient to show the nitroparaffin reacting as the carbanion IV or V, and an aldehyde reacting in the dipolar form (p. 274).



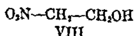
Nitroethane and propionaldehyde yield 2-nitro-3-pentanol.

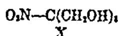


The products are nitroalcohols in which the two functional groups are attached to adjacent carbon atoms. Nitromethane is the most reactive of the nitroparaffins and may react with two molecules of aldehyde if the latter has less than five carbon atoms. The nitroalcohols on reduction yield amino alcohols. This is one of the most convenient methods for the synthesis of amino alcohols.

Formaldehyde, the most reactive unsubstituted aldehyde, often further. With nitromethane it gives the mono-, di-, and

tives, VIII, IX, and X, 2-nitroethanol, 2-nitro-1,3-propanediol, and 2-nitro-2-methylol-1,3-propanediol, respectively.





With other nitro compounds one or two molecules of formaldehyde may react. The trinitrate of X is known as "nib nitroglycerine." It is an explosive.

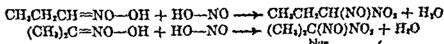
Nitroolefins sometimes are by-products in the formation of nitroalcohols; this is especially true with aromatic aldehydes when a tertiary amine is the catalyst.

4. *Halogenation.* The halogens react rapidly with aci-nitroparaffins or with a salt. The reaction is so rapid that it may be used for quantitatively determining the amount of aci form in equilibrium with the nitro form. For purposes of preparation a solution of the sodium salt gives good results. The product formed is an α-halogenated product.

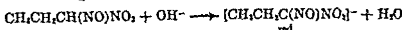


The chlorine and bromine compounds are stable, but the iodine compounds slowly decompose.

5. *Nitrosation.* Nitrous acid reacts with primary and secondary nitroparaffin, but not with tertiary. Reaction takes place at the α-position, preferably in the aci form.

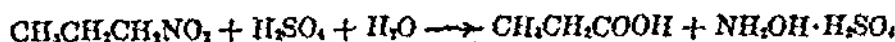


Primary nitroparaffins yield nitrolic acids, which rapidly form intensely red solutions with strong bases.

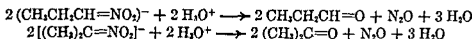


Secondary nitro paraffins yield pseudo nitroles, neutral substances of an intense blue color, and tertiary compounds do not react. The reaction is sometimes called the **red, white, and blue reaction.** It therefore distinguishes the three classes of aliphatic nitro compounds, and can be used also for distinguishing primary, secondary, and tertiary alkyl bromides or iodides and thus the corresponding alcohols. Formerly it was much used this way.

6. *Decomposition of salts of nitroparaffins.* When a salt of a primary nitroparaffin is warmed with concentrated acid, it decomposes into a carboxylic acid and a salt of hydroxylamine. The same result is obtained when a primary nitroparaffin is heated for some time with 85 per cent sulfuric acid.



When a solution of a salt of a nitroparaffin is added to an ice-cold, dilute (about 2.5 *M*) solution of a strong acid, nitrous oxide and an aldehyde or ketone are formed.



$$2\,(CH_3CH_2CH{=}NO_2)^- + 2\,H_3O^+ \longrightarrow 2\,CH_3CH_2CH{=}O + N_2O + 3\,H_2O$$
$$2\,[(CH_3)_2C{=}NO_2]^- + 2\,H_3O^+ \longrightarrow 2\,(CH_3)_2C{=}O + N_2O + 3\,H_2O$$

These two types of decomposition of nitroparaffins may become the basis of important industrial processes, especially for higher compounds. The main production of hydroxylamine sulfate now is from nitroparaffins

PROBLEMS

1. Write equations for the preparation of the following compounds.

a) 1-bromo-1-nitropropane
b) 1-chloro-1-nitrobutane
c) 2-bromo-2-nitrobutane
d) 2-chloro-2-nitropropane
e) 1-bromo-1-nitro-2-methylpropane
f) dibromonitromethane
g) bromochloronitromethane
h) 1,1-dichloro-1-nitroethane
i) 1-bromo-1-chloro-1-nitroethane
j) 1-chloro-1-nitro-2-methylpropane

2. Show how the following may be synthesized from compounds of fewer carbon atoms.

a) 2-nitro-1-propanol
b) 2-nitro-2-methyl-1,3-propanediol
c) 3-nitro-2-butanol
d) 3-nitro-2-pentanol
e) 1-amino-2-butanol
f) 1-nitro-3-methyl-2-butanol
g) 2-amino-1-ethanol
h) 2-nitro-3-pentanol
i) 2-nitro-1,3-propanediol
j) 1-amino-2-propanol
k) 2-nitro-1-butanol
l) 2-nitro-3-hexanol
m) 1-amino-2-butanol
n) 3-nitro-1,4-pentanediol
o) 2-nitro-3-methyl-1-propanol
p) 3-amino-2-hexanol

3. Starting with 1-nitrobutane, and using any other reagents, show the reaction steps (reagents and conditions are sufficient) by which the following may be prepared

a) 1-aminobutane
b) N-bromo-1-aminobutane
c) 1-acetamidobutane
d) 1-bromo-1-nitrobutane
e) 2-nitro-1-pentanol
f) 1-chloro-1-nitrobutane
g) 2-amino-1-pentanol
h) 1-nitro-1-nitrosobutane
i) 3-nitro-2-hexanol
j) 1-acetoxy-2-acetaminopentane
k) 2-nitro-2-*n*-propyl-1,3-propanediol
l) 2-acetoxy-3-acetamidohexane
m) *n*-butylhydroxylamine
n) 4-amino-3-heptanol
o) N,N′-di-*n*-butylurea
p) *n*-butylguanidine
q) *n*-butyramidoethane
r) *n*-butyraldehyde semicarbazone
s) acetaldoxime
t) ethyl *n*-butyrate
u) methyl-*n*-butylamine
v) *n*-butyronitrile

CHAPTER 25

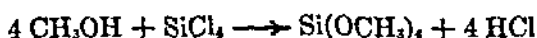
Compounds of Silicon

The element silicon occupies a position in the periodic table that places it in the carbon family. Like carbon, it is intermediate between a strongly electropositive element (sodium) and a strongly electronegative element (chlorine). The carbon-to-silicon bond is a typically purely covalent bond of low dipole moment and in this respect resembles the carbon-to-carbon bond.

Hydrosilicons: Silanes. The hydrides of silicon usually are called silanes, for example, silane, SiH_4; disilane, $H_3Si—SiH_3$; trisilane, $H_3Si—SiH_2—SiH_3$; etc. They form a homologous series that is analogous to the methane series of saturated hydrocarbons. The highest known member is hexasilane, Si_6H_{14}. This compound is not very stable and decomposes completely over a period of several months. The silicon-to-silicon bond becomes progressively less stable with increasing length, for disilane requires heating at 400 to 500° to cause decomposition. Silane requires heating to a red heat to cause decomposition into hydrogen and silicon. A mixture of silanes is formed when crude magnesium silicide is decomposed by mineral acids.

The completely chlorinated silanes are formed by the action of chlorine on silicon. The product is essentially silicon tetrachloride as the operation is usually carried out, but at relatively low temperature (about 150°) and slow flow, higher products up to decachlorotetrasilane, Si_4Cl_{10}, are obtained. These compounds resemble silicon tetrachloride in reactivity.

Silicon Tetrachloride and Silicate Esters. Silicon tetrachloride is remarkable for the ease with which it undergoes hydrolysis to silica and alcoholysis to esters of orthosilicic acid. It is a typical acid chloride and resembles the acid chlorides of strong acids rather than those of weak acids in the case of hydrolysis and alcoholysis The formation of methyl orthosilicate is typical.



$$4\ CH_3OH + SiCl_4 \longrightarrow Si(OCH_3)_4 + 4\ HCl$$

The esters, in turn, readily undergo hydrolysis under the proper conditions, for example, in a solvent that dissolves both water and the ester and contains a small amount of a catalyst such as sulfuric acid. Ethyl alcohol is a good solvent. Without a common solvent the hydrolysis usually proceeds quite

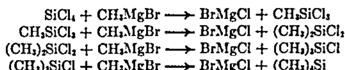
slowly because of the low mutual solubilities of water and esters, and the formation of silica at the interface of the two liquids.



$$2\,H_2O + Si(OCH_3)_4 \longrightarrow SiO_2 + 4\,CH_3OH$$

With an insufficient amount of water for complete hydrolysis, intermediate compounds are formed. These probably have a siloxane structure (see p. 410). With additional water, silica is slowly formed, at first in gel form. Orthosilicates are used as stone preservatives. They often are added to organic paints or lacquers to improve the hardness of the film.

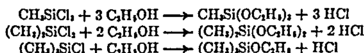
Organosilicon Compounds. An important group of these compounds is prepared from silicon tetrachloride. This may react with one, two, three, or four moles of Grignard reagent. The products resulting from the reaction with a methyl Grignard are, respectively, methyltrichlorosilane, dimethyldichlorosilane, trimethylchlorosilane, and tetramethylsilane (tetramethylsilicon). Other alkyl radicals may be attached to the silicon atom by the use of some other Grignard reagent. Other methods have been used, for example, alkylzincs or alkyl halides plus metallic sodium.



$$SiCl_4 + CH_3MgBr \longrightarrow BrMgCl + CH_3SiCl_3$$
$$CH_3SiCl_3 + CH_3MgBr \longrightarrow BrMgCl + (CH_3)_2SiCl_2$$
$$(CH_3)_2SiCl_2 + CH_3MgBr \longrightarrow BrMgCl + (CH_3)_3SiCl$$
$$(CH_3)_3SiCl + CH_3MgBr \longrightarrow BrMgCl + (CH_3)_4Si$$

Tetramethylsilane has properties remarkably like those of a hydrocarbon. It is an inert liquid, b.p. 26°, and quite stable when heated.

The chlorine compounds, like silicon tetrachloride, readily undergo hydrolysis, alcoholysis, and ammonolysis. The more important reactions are alcoholysis and hydrolysis.



$$CH_3SiCl_3 + 3\,C_2H_5OH \longrightarrow CH_3Si(OC_2H_5)_3 + 3\,HCl$$
$$(CH_3)_2SiCl_2 + 2\,C_2H_5OH \longrightarrow (CH_3)_2Si(OC_2H_5)_2 + 2\,HCl$$
$$(CH_3)_3SiCl + C_2H_5OH \longrightarrow (CH_3)_3SiOC_2H_5 + HCl$$

The products of alcoholysis — methyltriethoxysilane, dimethyldiethoxysilane, and trimethylethoxysilane, respectively — are stable compounds. They can be formed also by the action of a methyl Grignard or of dimethylzinc on ethyl orthosilicate.



$$Si(OC_2H_5)_4 + CH_3MgBr \longrightarrow CH_3Si(OC_2H_5)_3 + BrMgOC_2H_5\cdot$$

Other reactions proceed similarly. Other esters of silicic acid may be used and so also may other Grignard reagents, with the result that a large number of compounds of these general types can be prepared rather easily. The alkoxy compounds like the halogen compounds undergo hydrolysis readily.

Hydrolysis of a chloro or alkoxy compound might be expected to yield a hydroxy compound or its dehydration product, for example, $CH_3Si(OH)_3$ (methylsilanetriol) or CH_3SiOOH (methanesiliconic acid), $(CH_3)_2Si(OH)_2$ (dimethylsilanediol) or $(CH_3)_2SiO$ (dimethylsilicone), or $(CH_3)_3SiOH$ (trimethylsilanol). Of these compounds only the last has been isolated by a

special technique. It rapidly loses water to form a type of anhydride. Some compounds are known where the methyl is replaced by a larger group; for example, diphenylsilanediol, $(C_6H_5)_2Si(OH)_2$ is a stable white crystalline solid, and triphenylsilanol, $(C_6H_5)_3SiOH$, may be distilled at a temperature of 170 to 180° and a pressure of 1 mm. without change. In general, however, the hydroxy derivatives of the corresponding alkyl compounds are not known. The name *dimethyl silicone* was given originally to $(CH_3)_2SiO$ to indicate its resemblance to a ketone, $(CH_3)_2CO$, but chemically there is little resemblance.

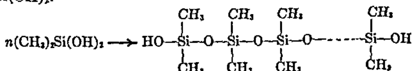
Siloxanes. The characteristic instability of silicic acid is carried over to the *silanols.* The pronounced tendency for two silicon atoms to be bonded through an oxygen atom by loss of water is exemplified by the trialkyl silanols, R_3SiOH.



$$2\,(CH_3)_3SiOH \longrightarrow (CH_3)_3Si{-}O{-}Si(CH_3)_3 + H_2O$$

The product from the hydrolysis of trimethylchlorosilane is hexamethyldisiloxane ($H_3Si{-}O{-}SiH_3$ is disiloxane, $H_3Si{-}O{-}SiH_2{-}O{-}SiH_3$ is trisiloxane, etc.).

Dialkylsilanediols, $R_2Si(OH)_2$, condense intermolecularly by loss of water to form polymers having many silicone units. Thus hydrolysis of dimethyldichlorosilane actually gives a product composed largely of dimethylsilicone units, $(CH_3)_2SiO$, formed from the unstable intermediate, dimethylsilanediol, $(CH_3)_2Si(OH)_2$.



$$n(CH_3)_2Si(OH)_2 \longrightarrow HO{-}\underset{CH_3}{\overset{CH_3}{Si}}{-}O{-}\underset{CH_3}{\overset{CH_3}{Si}}{-}O{-}\underset{CH_3}{\overset{CH_3}{Si}}{-}O{-}\cdots{-}\underset{CH_3}{\overset{CH_3}{Si}}{-}OH$$

This leads to the formation of high molecular weight linear polymers having a long siloxane chain, that is, a chain of silicon atoms bonded through oxygen. The polymeric products are oily substances of low solubility in many solvents.

Alkylsilanetriols, $RSi(OH)_3$, also form polymers. When R is small these are white silicalike solids, and when R is larger they may be glassy solids or even viscous products. The solid characteristics are due to the extensive cross linkage, since each silicon atom can form bonds through oxygen to three other silicon atoms. There is thus a three-dimensional network of siloxane linkages.

A mixture of trichloromethylsilane, CH_3SiCl_3, and dichlorodimethylsilane, $(CH_3)_2SiCl_2$, when hydrolyzed, gives a polymer in which the extent of cross linkage is proportional to the amount of trichloromethylsilane. As this is increased, the substance becomes progressively more viscous, then rubberlike and finally hard. The substitution of another alkyl group for methyl modifies the product also. A mixture of the corresponding trialkoxy and dialkoxy compounds gives similar results. It is possible to prepare a polymer tailor-made to suit a particular purpose.

Silicone resins find many uses. Exposure of surfaces to the vapor of substances like dimethyldichlorosilane leaves a water-repellent film. This pro-

cedure can be followed for causing the surfaces of numerous substances to be water repellent. These resins are remarkably stable towards heat and resistant to chemicals. Resins of proper flexibility are superior insulators for electrical equipment. Because silicone films can be much thinner than other kinds of insulation, equipment having much wiring, for example, motors, can be made much smaller.

PROBLEMS

1. Starting with *n*-propyl alcohol as the only organic compound, show the reaction steps involved in obtaining the following:

a) *n*-propyl orthosilicate
b) tri-*n*-propyl-*n*-propoxysilane
c) di-*n*-propyldichlorosilane
d) hexa-*n*-propyldisilane
e) tetra-*n*-propylsilane
f) *n*-propyltrichlorosilane
g) tri-*n*-propylchlorosilane
h) *n*-propyl-tri-*n*-propoxylsilane
i) hexa-*n*-propyldisiloxane
j) di-*n*-propyl-di-*n*-propoxysilane
k) di-*n*-propyl-*n*-propoxychlorosilane
l) hexa-*n*-propoxydisilane
m) hexa-*n*-propoxydisiloxane
n) 1,1,3,3-tetra-*n*-propyl-1,3-di-*n*-propoxydisiloxane

CHAPTER 26

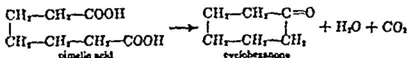
Derivatives of Cycloalkanes

Cyclohexane, cyclohexene, and cyclohexadiene form a connecting link between aliphatic and aromatic hydrocarbons (Chap. 27). Other interesting features of cycloalkane chemistry are the methods of ring closure and the stereochemistry of derivatives. Many naturally occurring substances have saturated or unsaturated ring systems, as for example, the musk ketones, the inositols, and the terpenes (see Chap. 43).

Methods of Ring Closure. The best methods of ring closure lead to the formation of derivatives of the cycloalkanes, rather than to the hydrocarbons themselves. The hydrocarbons usually can be obtained from these derivatives by suitable reactions.

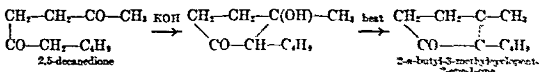
1. *Wurtz synthesis from α,ω-dibromoalkanes.* This method is mentioned in Chapter 7, and is satisfactory for the preparation of cyclopropane, cyclopentane, and cyclohexane sometimes with sodium, sometimes with zinc. Cyclobutane is obtained in only 7 per cent yield.

2. *Decarboxylation of α,ω-dibasic acids.* By this method, either the acid itself or some salt (calcium, barium, manganese, cerium, thorium, etc.) is pyrolyzed by methods previously mentioned (p. 188). Cyclopentanone is obtained in good yield by heating adipic acid with a small amount of manganous oxide. It is believed that the manganous salt decomposes more easily than the acid. Cyclohexanone can be obtained similarly from pimelic acid, but the yield is lower.



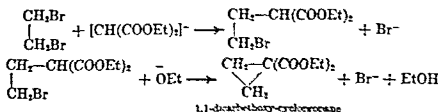
The yield of cyclic ketone decreases rapidly with lengthening of the carbon chain, and passes through a minimum at ten to eleven carbon atoms. Here the yield is only a fraction of a per cent. It rises to about 2 per cent at fifteen carbon atoms then drops again. The intermolecular reaction is the main reaction (p. 193). Cyclic ketones up to C_{34} ketones have been prepared this way.

3. *Intramolecular aldol condensation.* This can be accomplished with dialdehydes, diketones, and ketonic aldehydes. The reaction is of some importance with diketones because they are more available than the aldehydes.

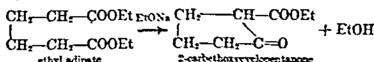


Reaction proceeds when the dione is boiled with dilute aqueous base. The product obtained results from dehydration.

4. *Intramolecular malonic ester condensation.* This is especially useful in the preparation of cyclopropane and cyclobutane derivatives, and gives satisfactory yields also of cyclopentane and cyclohexane derivatives (p. 332).

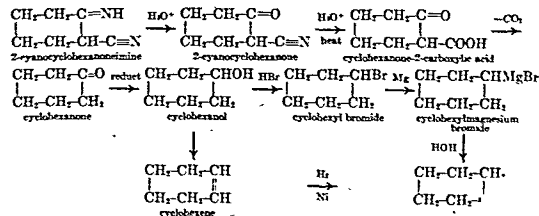


5. *Intramolecular Claisen condensation.* This works well for cyclopentane and cyclohexane derivatives, and can be adapted to the high dilution technique (p. 394). This is called the Dieckmann condensation.

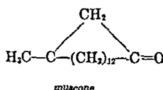


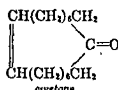
6. *Intramolecular dicyanide condensation.* This has proven, in the hands of Ziegler, to be the most useful general method, since it can be adapted easily to the high dilution technique (p. 394). Yields of cyclopentadecanone have been as high as 50 per cent, but here again the C_9, C_{10}, and C_{11} ring compounds are obtained in small yields of less than 1 per cent. Above C_{13} yields are good. All of the ketones up to C_{33}, with the exception of C_{27}, have been prepared.

Of the various methods available, this is the most convenient one for the synthesis of ketones of eight-membered and larger rings. It is useful also for cyclohexanone and other cyclohexane derivatives, starting with pimelonitrile (1,5-dicyanopentane), which gives 2-cyanocyclohexanoneimine on ring closure (p. 394).



Cyclic Ketones. The main interest in these compounds arises from their unusual odor. Muscone, the odiferous constituent of the secretion of the musk ox, is 3-methylcyclopentadecanone, and civetone, of the civet cat, is cycloheptadecene-10-one. These are the bases of typical musk perfumes.





Muscone is a ketone of a saturated fifteen carbon ring and civetone is a ketone of an unsaturated seventeen carbon ring. The desirable musk odor seems to be a maximum at fifteen carbon atoms.

Stereoisomerism. Both geometric (*cis,trans*) isomerism (pp 64, 200) and optical isomerism (p. 300) are observed with derivatives of the cycloparaffins. For the smaller ring systems the dicarboxylic acid derivatives are the best known examples. In addition to the 1,1-derivatives the possible stereoisomeric disubstituted cyclopropanes and cyclobutanes are shown by structures I to VIII, Figure 25. In the cyclopropane series, I is the *cis*-form

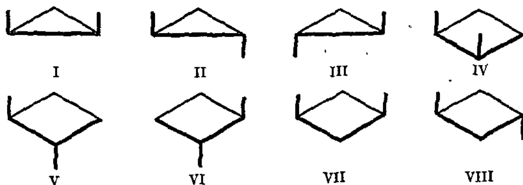


Figure 25 • Stereoisomeric Disubstituted Cyclopropanes and Cyclobutanes

and II and III are *trans*-forms. The ring plays the same role as a double bond in stereoisomerism of olefinic compounds (p. 64). The two *trans*-forms are mirror images of each other and cannot be superimposed. Formula I represents an internally compensated *meso*-form when the two substituents are alike, for there are two asymmetric carbon atoms in the molecule.

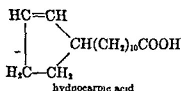
In the cyclobutane series, IV is the *cis*-1,2-isomer, and V and VI are *trans*-1,2-isomers, entirely analogous to the cyclopropane group. There are only geometric isomers of the 1,3-derivative, namely VII, *cis*, and VIII, *trans*. There are no optical isomers because there are no asymmetric carbon atoms in the molecule of the 1,3-isomer.

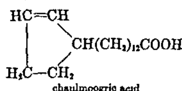
With larger rings there are more isomeric forms. In addition to the 1,1-derivatives there are three 1,2- and three 1,3-cyclopentane derivatives, three 1,2-, three 1,3- and two 1,4-cyclohexane derivatives, when the groups are alike. With unlike groups, optical isomerism is possible for most of the *cis*-forms.

TABLE 77 | Some Derivatives of Cyclopentane and Cyclohexane

	B.P. °C		M.P. °C	B.P. °C
Cyclopentane	50	Cyclohexane	6.5	81
Cyclopentene	45–46	Cyclohexene		83
Cyclopentadiene	41–42	1,3-Cyclohexadiene		80.5
Cyclopentanol	139–140	1,4-Cyclohexadiene		86–87
Cyclopentanone	130	Cyclohexanol	24	161
Cyclopentyl bromide	137–139	Cyclohexanone	−45	155
		Cyclohexyl bromide		163–165

Hydnocarpic and Chaulmoogric Acids. These acids, present as glycerides in chaulmoogra oil, are derivatives of cyclopentene.


hydnocarpic acid


chaulmoogric acid

The therapeutic value of chaulmoogric oil in the treatment of leprosy is due to the presence of these two acids, which also by themselves are valuable for this purpose.

CYCLOHEXANE DERIVATIVES

Cyclohexanol, $C_6H_{11}OH$. The most convenient method for the preparation of this is *by catalytic hydrogenation of phenol (p. 497) at 140 to 160° in the presence of* nickel.



$$C_6H_5OH + 3\,H_2 \longrightarrow C_6H_{11}OH$$

Also it may be obtained by reduction of cyclohexanone. Cyclohexanol is a typical secondary alcohol. With hydrobromic acid it yields cyclohexyl bromide; with acetic anhydride, cyclohexyl acetate; and with a suitable oxidizing agent, cyclohexanone. When heated with sulfuric acid, it is converted into an unsaturated hydrocarbon, cyclohexene.



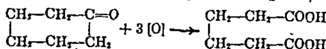
$$C_6H_{11}OH \longrightarrow C_6H_{10} + H_2O$$

Cyclohexanone, $C_6H_{10}O$. This is prepared by pyrolysis of pimelic acid (p. 189), by other ring closure methods (p. 413), or by the regulated oxidation of cyclohexanol with chromic acid mixture or other suitable oxidizing agent.



$$C_6H_{11}OH + [O] \longrightarrow C_6H_{10}O + H_2O$$

It is a typical ketone. With hydroxylamine, it yields an oxime (m.p. 90–90.5°); with sodium and water it is reduced to cyclohexanol; and with a strong oxidizing agent (nitric acid or alkaline permanganate) it is oxidized to adipic acid, by scission of a carbon-to-carbon bond, as in the case of an acyclic ketone (p. 276).



Th... ufacturing adipic acid, ... Other newer methods are now available (see Furan, Chap. 41).

***Inositol*, Hexahydroxycyclohexane, $C_6H_6(OH)_6$.** Inositol occurs widely distributed in nature. One form, an optically inactive, internally compensated (nonresolvable) form, m p 217 to 218°, is present in the leaves, seeds, and fruits of a very large number of plants, especially in unripe seeds and fruits. Usually it disappears as the ripening process develops, for it becomes transformed into sugar. Monomethyl ethers of the only two possible active forms also occur; one ether, pinitol, found in a pine, *Pinus lambertiana* Douglas, gives (+)-inositol on hydrolysis; a second, quebrachitol, in the sap of the rubber tree, *Hevea braziliensis*, gives (−)-inositol on hydrolysis. The two active inositols are shown in Figure 26.

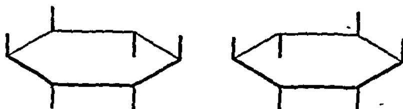


Figure 26 · Optically Active Inositols

Hexachlorocyclohexane, $C_6H_6Cl_6$, and Hexabromocyclohexane, $C_6H_6Br_6$. These are formed by the action, in sunlight, of the respective halogen on benzene (p. 421). They are often called benzene hexachloride and benzene hexabromide, respectively. The former is widely used as an insecticide (chlordane).

Cyclohexene, Cyclohexadiene, and Cyclohexatriene (Benzene). The preparation of unsaturated hydrocarbons, having a ring of six carbon-atoms is outlined in Figure 27.

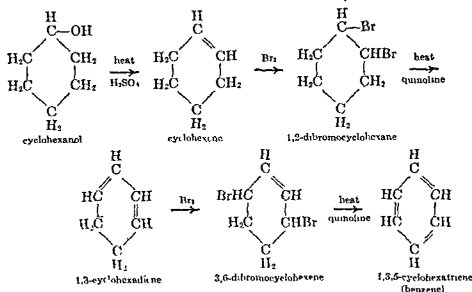


Figure 27 · Benzene from Cyclohexanol

Cyclohexanol when heated with sulfuric acid yields cyclohexene and this readily add bromide to give the corresponding bromide, 1,2-dibromocyclohexane. When this

heated for a long time with quinoline, a tertiary base (b.p. 238°), two molecules of hydrogen bromide are removed with formation of two double bonds. The reaction product, 1,3-cyclohexadiene, adds one molecule of bromine to yield 3,6-dibromocyclohexene by 1,4-addition, just as 1,3-butadiene does (p. 89). Elimination of two molecules of hydrogen bromide from this dibromide by heating with quinoline gives a molecule having three conjugated double bonds, benzene. The conversion of cyclohexanol to benzene is a confirmation of the relationship of benzene to cyclohexane, known from other investigations.

TABLE 78 **Hydrogenation of Cycloalkenes to Cyclohexane**
(Kistiakowsky)

HYDROCARBON	ΔH KCAL./MOLE	ΔH OF FIRST DOUBLE BOND KCAL./MOLE	ΔH PER DOUBLE BOND KCAL./MOLE	ΔH CALCULATED FOR ISOLATED D B. KCAL./MOLE	ΔH OF STABILIZATION KCAL./MOLE
Cyclohexene	−28.59	−28.6	−28.6	−28 6 [a]	
Cyclohexadiene-1,3	−55 37	−26.8	−22.7	−57.2	−1.8
Cyclohexatriene-1,3,5 (benzene)	−49 80	+5.6	−16.6	−85 8	−36.0

[a] ΔH, for *cis*-2-butene, −28.45 kcal./mole.

Heats of Hydrogenation. In Table 78 are listed the heats of hydrogenation of cyclohexene, 1,3-cyclohexadiene, and benzene to cyclohexane, that is, complete reduction. The observed ΔH of hydrogenation of cyclohexene to cyclohexane, *viz.*, −28.59 kcal., is remarkably close to ΔH of hydrogenation of *cis*-2-butene, *viz.*, −28.45 kcal. This shows that the ring structure of cyclohexene does not have any significant effect on the heat of the reaction.

The hydrogenation of cyclohexadiene to cyclohexane liberates 55.37 kcal. This includes two reactions, that of the diene to the cycloalkene, and of the cycloalkene to the cycloalkane. Since for the latter step ΔH is −28.59, ΔH of the former step is the difference, *viz.*, −26.78 kcal.

Likewise, three steps are involved in the hydrogenation of benzene to cyclohexane: the first is the formation of cyclohexadiene, the second that of cyclohexene, and the third that of cyclohexane. Since ΔH of the last two steps is −55 37 kcal., that of the first step is the difference between −49.80 and −55.37, *viz.*, +5 6 kcal. This is an extraordinary result, for it shows that it would be necessary for energy to be absorbed if only one molecule of hydrogen were to add to one molecule of benzene.

Another interesting conclusion is reached if the actual heats of hydrogenation are compared with the values expected if the double bonds had no effect on each other, that is, if they were isolated double bonds. These values are shown in the next to last column of Table 78. The difference between these values and the experimental values are shown in the last column. These represent the degree to which the diene and triene are more stable than they would be if the double bonds were isolated from each other. Since the double bonds are conjugated, these values are the conjugation energies, or the resonance energies of stabilization of the respective hydrocarbons. Thus ΔH of stabilization of cyclohexadiene is −1.8 kcal, and of benzene −36 0 kcal.

These energy relationships are important in connection with the chemistry of benzene and its derivatives.

PROBLEMS

1. Write equations for reactions involved in a satisfactory preparation of the following from pimelic acid:

a) cyclohexanone
b) cycloheptanone
c) cyclooctanone
d) 2-carboxycyclohexanone
e) 2-carbethoxycyclohexanone
f) 2-carboxycycloheptanone
g) 1,1-dicarbethoxycyclooctanone
h) 2-carbethoxycycloheptanone
i) 2-carbethoxycyclooctanone
j) adipic acid

2. Starting with ethanol and 1,4-butanediol as the only organic compounds (not including sodium cyanide), show the reaction steps (reagents, conditions, and arrows are sufficient) involved in the preparation of:

a) carboxycyclopentane
b) 1,1-dicarbethoxycyclopentane
c) ethyl cyclopentanecarboxylate
d) 1,4-dicyclopentyloxybutane
e) cyclopentane
f) cyclopentanone
g) cyclopentanol
h) cyclopentyl bromide
i) methylcyclopentyl carbinol
j) 1-ethylcyclopentanol
k) monocyclopentyl succinate
l) dicyclopentyl succinate
m) 2-cyanocyclopentanone
n) 2-carboxycyclopentanone
o) dicyclopentyl adipate
p) cyclopentene
q) 1,2-dibromocyclopentane
r) 2-carbethoxycyclopentanone
s) 1,4-cyclopentyl-1,4-butanedione
t) bicyclopentyl
u) 1-hydroxybicyclopentyl

3. Show the theoretically possible stable isomeric and stereoisomeric forms of the following and state which forms possess optical activity.

a) dimethylcyclopropane
b) dimethylcyclobutane
c) trimethylcyclopropane
d) trimethylcyclobutane
e) methylethylcyclopropane
f) methylethylcyclobutane
g) dimethylethylcyclopropane
h) dimethylethylcyclobutane
i) dihydroxycyclopentane
j) dihydroxycyclohexane
k) bromomethylcyclopentane
l) bromomethylcyclohexane
m) methylcyclobutanone oxime
n) methylcyclopentylpropene
o) cyclopentyl lactate
p) dicyclohexyl malate
q) monocyclohexyl tartrate
r) dicyclohexyl tartrate
s) monocyclohexyl citrate
t) tricyclopentyl citrate
u) 1,2,4-trichlorocyclohexane
v) 1,2,3,4,5,6-hexabromocyclohexane

CHAPTER 27

Aromatic Hydrocarbons

In the period 1830–1840, Liebig and Wöhler found that the benzoyl radical was a component of a number of "aromatic" organic compounds possessing agreeable aromatic odors, especially benzaldehyde and benzoic ester. This led to the adoption of the expression *aromatic* for benzene and its derivatives, as distinct from *aliphatic*, for compounds related to fats. The former name has lost its original significance, because numerous benzene derivatives have no odor and numerous aliphatic compounds have.

Aromatic hydrocarbons are found widely distributed in petroleums. In the paraffinic type the amount present is relatively small, up to 10 per cent; but there are some heavy petroleums in which the content of aromatic hydrocarbons is as high as 40 per cent. One of the main sources of aromatic hydrocarbons is coal tar. Dehydrogenation of cyclohexane is an industrial method for benzene, and cyclization of petroleum products is an industrial process for benzene and toluene (p. 56).

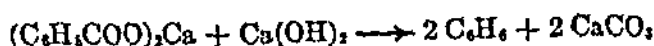
Coal Tar. When coke is made in a by-product coke oven, coal is heated without air until all the volatile decomposition products are driven out. The solid residue of carbon and mineral matter is the coke. The volatile materials are also recovered. These include a gas, water, ammonia, aromatic hydrocarbons (benzene, toluene, xylene, naphthalene, anthracene, etc.), oxygenated compounds (phenol, cresol, etc.), and nitrogenous compounds (pyridine, picoline, quinoline, etc.). The gas, largely a mixture of methane and hydrogen, is used for illumination. The remaining organic material forms a water-insoluble phase called coal tar. High temperature pyrolysis of coal (*ca.* 1000° C) produces more gas and less coal tar than low temperature pyrolysis (*ca.* 500°). However, low temperature coal tar contains some aliphatic hydrocarbons.

Coal tar is separated into its components by a combination of distillation and extraction. In the classical method of distillation, a separation is made into crude fractions, approximately as follows: (1) light oils, up to 170–200°; (2) middle oil, or creosote oil, 170–200° to 230–250°; (3) heavy oil, 230–250° to 270–300°; (4) anthracene oil, 270–300° to 340–350°; pitch, the residium. The designation light oil includes also the material recovered from the gas.

Stirring the individual fractions with cold *concentrated* sulfuric acid extracts the oxygen and nitrogen compounds. The organic phases, now composed mainly of hydrocarbons, are subjected to careful fractional distillation so as to obtain the components reasonably pure. Within recent years continuous distillation methods are supplanting the older batch methods, leading to reasonably pure products in one distillation. Different types of coal differ in the amount of coal tar obtained. A soft coal (bituminous) yields much more than a hard coal (anthracite). The main components of coal tar are: benzene and toluene, 1 to 1.5 per cent; phenol, 0.5 to 1.0 per cent; cresols, 1 to 2 per cent, naphthalene, 6 to 10 per cent; methyl and dimethylnaphthalenes, 3 to 5 per cent; anthracene, 1 per cent; phenanthrene, 2 to 4 per cent; heavy oil, 25 to 30 per cent; pitch, 50 to 60 per cent. More than 120 organic compounds, mostly aromatic, have been isolated from coal tar.

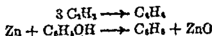
Germany led in the development of the coal tar industry and up to the advent of World War I had a virtual monopoly. Subsequently, however, the production of coal tar increased rapidly in the United States, and an important industry based upon coal tar has developed in this country.

Benzene, Benzol, C_6H_6. This hydrocarbon was discovered by Faraday in 1825 as one of the constituents of the liquid obtained by compressing coal gas. Leigh (1842) found benzene in coal tar. Benzene is present in many petroleums. It was first synthesized by Mitscherlich in 1833, who heated benzoic acid with lime.



$$(C_6H_5COO)_2Ca + Ca(OH)_2 \longrightarrow 2\,C_6H_6 + 2\,CaCO_3$$

Benzene is obtained when acetylene is heated under pressure, or when phenol vapor is passed over heated zinc dust.



$$3\,C_2H_2 \longrightarrow C_6H_6$$
$$Zn + C_6H_5OH \longrightarrow C_6H_6 + ZnO$$

It has been obtained from cyclohexene by a succession of brominations and dehydrobrominations (p. 417), and is formed when cyclohexane undergoes dehydrogenation by passage over metallic catalysts (platinum, nickel, etc.), near 300°.



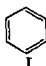
$$C_6H_{12} \longrightarrow C_6H_6 + 3\,H_2$$

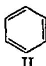
Benzene is present in the complex products resulting from the high temperature treatment of paraffin hydrocarbons, conditions that promote a number of changes such as decomposition, pyrolysis, and recombination (p. 56).

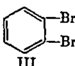
Benzene, b.p. 80.12°, is a colorless, mobile liquid, soluble in most organic liquids, insoluble in water and in concentrated sulfuric acid. As obtained from coal tar it contains a small amount of thiophene (C_4H_4S, b.p. 84°), from which it is separated by shaking with cold, *concentrated* sulfuric acid. This removes the thiophene through a sulfonation reaction, and the sulfonated product dissolves in the acid. Benzene is a poison; the breathing of its vapor in low concentration over considerable periods of time causes anemia and in high concentrations even for a short time may cause death. Benzene has a higher solvent action than hexane on numerous organic compounds. On this

account benzene finds extensive use as a solvent. It is sometimes added to motor fuel, because of its high antiknock value (Table 30, p. 101). It is a starting substance for the manufacture of numerous compounds, for example, nitrobenzene, aniline, phenol, salicylic acid, and aspirin, and for many types of dyes, for example, azo dyes, rosaniline dyes, indigo dyes, and others.

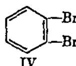
The Kekulé Structure of Benzene. In 1865 the German chemist, Kekulé, proposed a cyclic structure for benzene. In this there are six carbon atoms in the ring, and the six bonds are alternate single and double bonds, I or II. It was early recognized that this structure was inadequate because it predicts the existence of two isomeric 1,2-dibromo substitution products, III and IV. All efforts to prepare two such compounds failed. Kekule later modified his structure by assuming that there is a rapid oscillation of the bonds of the benzene ring, the single bonds changing to double, and *vice versa.* Thus he represented benzene by I *and* II, and 1,2-dibromobenzene by III *and* IV. The rapid oscillation of the bonds accounted for the observation that there is only one 1,2-dibromobenzene. A consequence of the Kekulé model is a planar molecule, and this is known to be the case.


I


II



III

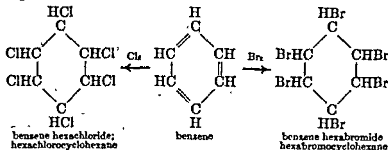


IV

The announcement of the ring structure of benzene by Kekulé was an important event in the history of organic chemistry. It suggested numerous researches of both theoretical and practical value and laid a sound basis for the development of aromatic chemistry, a process still going strong even today.

Reactions of Benzene. In its general behavior benzene acts like a saturated hydrocarbon. It does not react readily with aqueous permanganate even when heated, and it does not readily decolorize bromine. The typical reactions of benzene are of two general types, addition and substitution, of which the latter is by far the more important. The principal addition reactions are those with chlorine and bromine (illumination necessary; slow even then) and hydrogen (catalyst necessary). The principal substitution reactions are those of halogenation (catalyst necessary), sulfonation (more rapid than with alkanes), nitration (ditto), and alkylation (catalyst necessary).

1. *Addition of halogens.* In sunlight, benzene adds chlorine and bromine slowly; the addition compounds are dissolved in a much larger quantity of substitution products.



These addition compounds are substitution products of cyclohexane. These reactions are of theoretical significance because they prove that the carbon atoms of benzene are joined in a ring.

2. *Addition of hydrogen; hydrogenation.* Benzene is hydrogenated at room temperature in the presence of platinum or at 80 to 180° in contact with nickel (Table 78, p. 417).

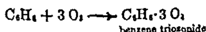


$$3\,H_2 + C_6H_6 \longrightarrow C_6H_{12} \quad \Delta H = -49.8 \text{ kcal.}$$

The reduction of benzene to cyclohexane was first accomplished in 1877 by the use of hydriodic acid. The reduction to cyclohexane, unknown to Kekulé in 1865, substantiated the ring structure of and the presence of three double bonds in the molecule of benzene.

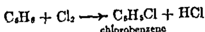
The reaction is reversible, and at temperatures of 300° or higher cyclohexane is dehydrogenated to benzene. Even at 300°, however, benzene can be hydrogenated at high pressures, the increase in pressure opposing the effect of increase in temperature.

3. *Addition of ozone.* Benzene adds ozone to form a triozonide. This reaction confirms the presence of three double bonds in the benzene molecule.

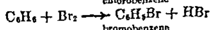


$$C_6H_6 + 3\,O_3 \longrightarrow \underset{\text{benzene triozonide}}{C_6H_6 \cdot 3\,O_3}$$

4. *Halogenation.* Benzene reacts with chlorine or bromine in the presence of a catalyst or carrier to form substitution products. The most active catalysts are anhydrous aluminum chloride and bromide; less active are the anhydrous ferric salts, iodine, and pyridine.

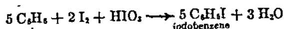


$$C_6H_6 + Cl_2 \longrightarrow \underset{\text{chlorobenzene}}{C_6H_5Cl} + HCl$$



$$C_6H_6 + Br_2 \longrightarrow \underset{\text{bromobenzene}}{C_6H_5Br} + HBr$$

Iodine will substitute when an oxidizing agent like iodic acid or nitric acid is added and the mixture is heated in a sealed tube.



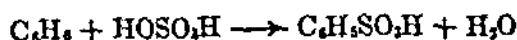
$$5\,C_6H_6 + 2\,I_2 + HIO_3 \longrightarrow \underset{\text{iodobenzene}}{5\,C_6H_5I} + 3\,H_2O$$

In the presence of anhydrous ferric halides, all of the hydrogen atoms may be substituted, with the formation of hexabromobenzene.



$$C_6H_6 + 6\,Br_2 \longrightarrow C_6Br_6 + 6\,HBr$$

5. *Sulfonation.* Concentrated sulfuric acid reacts slowly, fuming sulfuric acid more rapidly, with the production of benzenesulfonic acid.



$$C_6H_6 + HOSO_3H \longrightarrow C_6H_5SO_3H + H_2O$$

This reaction is typical of aromatic hydrocarbons.

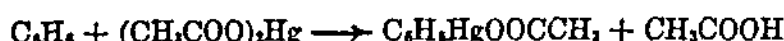
6. *Nitration.* Concentrated nitric acid reacts slowly, and anhydrous (fuming) nitric acid reacts rapidly with benzene, the product being nitrobenzene. This is the most important reaction of benzene and its derivatives.



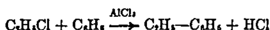
$$C_6H_6 + HONO_2 \longrightarrow C_6H_5NO_2 + H_2O$$

The usual nitrating acid is a mixture of concentrated nitric and concentrated sulfuric acids. A second nitro group may be introduced (p. 460). Attempt to introduce a third group into benzene usually results in oxidation.

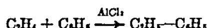
7. *Mercuration.* When benzene is heated with mercuric acetate in acetic acid solution, a product is formed in which mercury is directly joined to a carbon atom, *viz.*, phenylmercuric acetate.



8. *Alkylation.* There are two main alkylation reactions, *viz.*, with alkyl halides and with olefins. When an alkyl halide (ethyl chloride, for example) is added to benzene and anhydrous aluminum chloride, hydrogen chloride is evolved and ethylbenzene is formed (Friedel-Crafts reaction).



In industry a mixture of ethylene and benzene is passed under pressure over aluminum chloride at 93° (200° F), to give ethylbenzene.

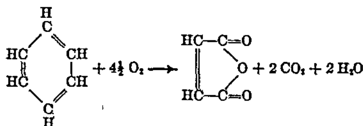


9. *Coordination with silver ion.* Benzene is much more soluble in aqueous silver nitrate than it is in aqueous potassium nitrate or in water. The increased solubility is due to the formation of a loose coordination complex between benzene and silver ion. It resembles the complex between an olefin and silver ion (p. 133) but is less stable.



It is probable that similar coordination complexes are formed as the first step in the reaction of benzene with other reagents, as, for example, in the nitration of benzene.

10. *Oxidation.* Benzene is oxidized when the vapor mixed with air is passed over vanadium pentoxide at 400°. By regulating the amount of oxygen, maleic anhydride can be obtained in good yield. This reaction would seem to indicate the presence of at least one double bond in the benzene molecule.



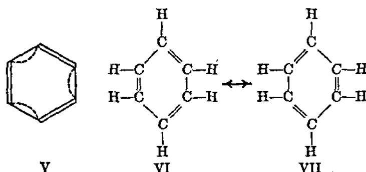
Structure of Benzene. A correct structure of benzene must offer a satisfactory explanation of certain well-established facts as follows:

1. Benzene acts like a saturated compound towards many reagents, as, for example, permanganate and the halogens.

2. In its ability to add halogens, hydrogen, and ozone, benzene resembles an unsaturated compound.
3. One and only one monobromobenzene is known.
4. Three and only three dibromobenzenes are known.

Extensions of the Kekulé Structure of Benzene. These rather contradictory properties of benzene, *i.e.*, its apparently saturated character with some reagents and unsaturated character with others led to much speculation and other structures. The best of these before the development of the theory of resonance was that proposed by Thiele. He considered that the alternate arrangement of single and double bonds of the benzene ring constitutes a closed conjugate system, which he represented as V. Here the dotted lines represent mutual saturation of adjacent unsaturated carbon atoms (p. 89). The bonds around the benzene ring are thus more alike than are the single and double bonds of the Kekulé model.

The benzene problem can now be regarded as satisfactorily solved. In his development of the theory of resonance as applied to organic compounds, Pauling has shown that the possibility of resonance between the two Kekulé structures (and to a minor extent other structures) accounts in a large measure for the high stability of benzene. Thus benzene is regarded as a hybrid structure to which the two Kekulé forms, VI and VII, contribute most. The Thiele formula, V, is a remarkably close approximation to the modern one.



The enhanced stability of benzene (39 kcal.) in comparison to its stability calculated from bond energies is explained as arising from resonance.

The chemical inertness of the double bonds of benzene towards such reagents as chlorine, bromine, and permanganate, reagents that react rapidly with typical olefinic double bonds, also can be explained on the basis of resonance. It is shown in Table 78, page 417, that energy must be absorbed for benzene to be converted into cyclohexadiene. Once the stable benzene structure is converted to that of cyclohexadiene, however, reaction would take place rapidly, because cyclohexadiene is a typical unsaturated compound. Thus, in the slow reaction of benzene with chlorine or bromine in sunlight, the addition compounds usually isolated are those formed by reaction with three molecules of halogen. Recently, benzene tetrachlorides have been isolated as intermediates.

Bond Distances Between Carbon Atoms. Each carbon-to-carbon bond in benzene is regarded as having 50 per cent single-bond character and 50 per cent double-bond character. In graphite each bond is considered to have one-third double-bond character and two-thirds single bond character.

The carbon-to-carbon distance in benzene is 1.39 Angstrom units and in graphite is 1.42 Å. The single-bond distance is 1.54 Å and the double-bond distance is 1.34 A. By plotting the distance against the amount of single-bond character, a curve is obtained (Pauling) which shows graphically how increase in unsaturated character produces bond shortening (Fig. 28). The

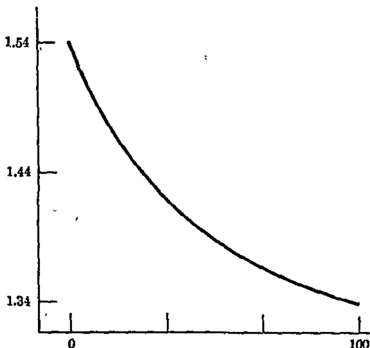
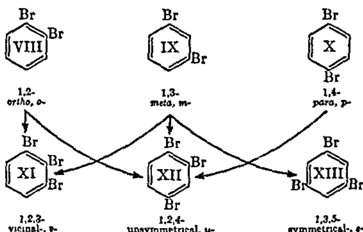


Figure 28 • Plot of C–C Distance against Per Cent of Double Bond Character

plot can be extended to include the triple bond. The value of this plot lies in the possibility of estimating the amount of unsaturated character in a carbon-to-carbon bond from the separation distance. It follows, therefore, that relative inertness of the double bonds of benzene can be explained on the basis that they are hybrid bonds possessing only 50 per cent double-bond character.

The Isomerism of Benzene Derivatives. One monobromo, three dibromo, three tribromo, three tetrabromo, one pentabromo, and one hexabromobenzene are predicted by the Kekulé formula, and all are known. They may be named either by the numbering method or by special names, as illustrated in the case of the di- and trisubstituted compounds. Since the prefixes, *ortho*, *meta*, and *para* are much employed to indicate the 1,2-, 1,3-, and 1,4-*disubstituted* benzenes, *respectively*, the student should familiarize himself with them. The 1,2,3-, the 1,2,4-, and the 1,3,5-tribromobenzenes sometimes are designated as vicinal, unsymmetrical, and symmetrical, respectively.

Orientation of Dibromo and Tribromobenzenes. Koerner, in 1874, settled the question of orientation by the so-called **absolute method.**

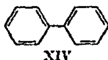


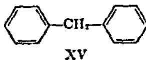
He established relationships between the three dibromo and the three tribromo derivatives, mainly through the nitrodibromo compounds. This was accomplished by reducing the nitro group to the amino group and replacing it with either hydrogen or with bromine through the diazo reaction (Chap. 32), thus yielding either a dibromo or a tribromo compound. The relationships can be simplified by stating that they are the same as if the dibromo compounds were converted into the tribromo compounds by direct bromination. Direct bromination was not practical in all cases, because separation of the compounds from the reaction mixtures is difficult and in some cases almost impossible, especially when one isomer is present in small amount.

The relationships may be summarized as follows: the dibromobenzene melting at 87° is related to only one tribromobenzene; the one melting at 6°, to two; and the one melting at −6.9°, to three. Thus the highest melting dibromide is *para*, X, the lowest melting is *meta*, IX, and the other is *ortho*, VIII. One tribromobenzene, m.p. 44°, is related to three dibromobenzenes, and this is the 1,2,4-derivative, XII; the one melting at 88° is related to two and thus is the 1,2,3-isomer, XI, and the tribromobenzene related to only one dibromobenzene is the 1,3,5-isomer, XIII, melting at 120°. The relationships are shown above by arrows.

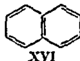
From the known dibromobenzenes it is possible to obtain the xylenes and from these, by oxidation, the dicarboxylic acids. Other compounds can be related to these.

Types of Aromatic Hydrocarbons. The simplest types are benzene homologs, C_nH_{2n-6}, having one benzene ring and one or more saturated aliphatic **side chains.** Another type may be unsaturated, with one or more double or triple bonds in the side chains. Still other types may have more than one benzene ring in the molecule. The main divisions of the last are: (1) two or more benzene nuclei directly joined, as in biphenyl, XIV; (2) two or more benzene nuclei attached to one or more aliphatic carbon atoms, as in diphenylmethane, XV; (3) two or more fused benzene rings, *i.e.*, two carbon atoms common to two nuclei, as in naphthalene, XVI.


XIV



XV


XVI

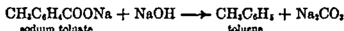
Description of hydrocarbons having two or more benzene rings is deferred until after the characteristic reactions of benzene and homologs have been studied.

HOMOLOGS OF BENZENE

A number of benzene homologs occur in coal tar. The most important are toluene, $C_6H_5CH_3$, and the xylenes, $C_6H_4(CH_3)_2$. Others are ethyl benzene, and all of the trimethyl and tetramethyl derivatives. The radicals of aromatic hydrocarbons, with the exception of that of benzene, are named from the hydrocarbon; for example, C_6H_5— is **phenyl**, CH_3—C_6H_4— is **tolyl**, $(CH_3)_2C_6H_3$— is **xylyl**, etc. These are **aryl** radicals; the attachment is directly to the aromatic ring. An aliphatic radical attached to the benzene ring is often called a side chain. An example of a radical that resembles an alkyl radical, *i.e.*, an arakyl radical, is $C_6H_5CH_2$—, benzyl.

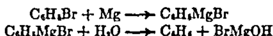
Preparation of Aromatic Hydrocarbons. These may be obtained by reactions in which certain groups attached to the benzene ring are eliminated.

1. *Decarboxylation.* This occurs, as in the aliphatic series, when a salt is heated with soda lime.



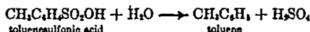
$$\underset{\text{sodium toluate}}{CH_3C_6H_4COONa} + NaOH \longrightarrow \underset{\text{toluene}}{CH_3C_6H_5} + Na_2CO_3$$

2. *Removal of halogen.* One of the most convenient methods is through the Grignard reagent. Sometimes hydrogen (with a catalyst) will remove halogen.



$$C_6H_5Br + Mg \longrightarrow C_6H_5MgBr$$
$$C_6H_5MgBr + H_2O \longrightarrow C_6H_6 + BrMgOH$$

3. *Removal of sulfonic acid group.* When a sulfonic acid is heated with water at 150 to 200°, a reversal of the sulfonation reaction occurs.



$$\underset{\text{toluenesulfonic acid}}{CH_3C_6H_4SO_2OH} + H_2O \longrightarrow \underset{\text{toluene}}{CH_3C_6H_5} + H_2SO_4$$

This reaction is especially useful for removing a sulfonic acid group introduced to block off some particular position during a reaction (p. 457).

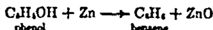
4. *Removal of the diazonium group.* Sometimes alcohol is an effective reagent.



$$C_2H_5OH + \underset{\text{benzenediazonium chloride}}{C_6H_5N_2Cl} \longrightarrow \underset{\text{benzene}}{C_6H_6} + N_2 + HCl + CH_3CHO$$

The diazonium group is formed from an amino group by the action of sodium nitrite and a strong acid (Chap. 32).

5. *Removal of oxygen from phenol.* This can be done by passing the vapor of a phenol over heated zinc dust or hot iron filings (p. 497).



$$\underset{\text{phenol}}{C_6H_5OH} + Zn \longrightarrow \underset{\text{benzene}}{C_6H_6} + ZnO$$

6. *Changing a ketone side chain to an alkyl side chain.* This is done by heating with amalgamated zinc and hydrochloric acid.

$$2\,Zn + 4\,HCl + \underset{\text{ethyl phenyl ketone}}{C_6H_5COC_2H_5} \longrightarrow \underset{n\text{-propylbenzene}}{C_6H_5CH_2C_2H_5} + 2\,ZnCl_2 + H_2O$$

The reaction is especially useful when a normal side chain is desired.

Preparation of Benzene Homologs. Attachment of side chains to the benzene ring can be accomplished by different methods.

1. *The Wurtz-Fittig synthesis* (developed by Wurtz in the aliphatic series and by Fittig in the aromatic).

$$\underset{\text{bromobenzene}}{C_6H_5Br} + 2\,Na + \underset{\text{1-bromobutane}}{Br(CH_2)_3CH_3} \longrightarrow \underset{n\text{-butylbenzene}}{C_6H_5(CH_2)_3CH_3} + 2\,NaBr$$

2. *The Grignard synthesis.* An allyl side chain may be attached to the benzene ring in a reaction between an aryl Grignard reagent and allyl bromide; in case a benzyl Grignard reagent is used, the side chain is lengthened by reaction with allyl bromide, or with a very reactive alkylating agent (sulfate ester).

$$\underset{\text{phenylmagnesium bromide}}{C_6H_5MgBr} + \underset{\text{allyl bromide}}{BrCH_2CH{=}CH_2} \longrightarrow \underset{\text{allylbenzene}}{C_6H_5CH_2CH{=}CH_2} + MgBr_2$$

$$\underset{\text{benzylmagnesium bromide}}{C_6H_5CH_2MgCl} + BrCH_2CH{=}CH_2 \longrightarrow \underset{\text{4-phenyl-1-butene}}{C_6H_5CH_2CH_2CH{=}CH_2} + MgBrCl$$

$$C_6H_5CH_2MgCl + (C_2H_5)_2SO_4 \longrightarrow \underset{n\text{-propylbenzene}}{C_6H_5CH_2CH_2CH_3} + C_2H_5OSO_2MgCl$$

For a radical larger than ethyl sometimes the ester of benzenesulfonic acid (or toluenesulfonic acid) is used.

$$C_6H_5CH_2MgCl + 2\,ROSO_2C_6H_5 \longrightarrow C_6H_5CH_2R + (C_6H_5SO_2O)_2Mg + RCl$$

An unsaturated side chain may be reduced to an alkyl side chain, to give the benzene homolog.

3. *The Friedel-Crafts synthesis.* Alkyl halides, in the presence of anhydrous aluminum chloride, react with benzene to form alkylated benzenes.

$$\underset{\text{benzene}}{C_6H_6} + \underset{\text{ethyl chloride}}{C_2H_5Cl} \xrightarrow{AlCl_3} \underset{\text{ethyl benzene}}{C_6H_5C_2H_5} + HCl$$

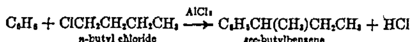
The reaction product is a mixture because the monoalkylated compound reacts with more alkyl halide forming di- and polyalkylated benzenes.

$$C_6H_5C_2H_5 + C_2H_5Cl \xrightarrow{AlCl_3} C_6H_4(C_2H_5)_2 + HCl$$

There are other complications. Aluminum chloride in the presence of hydrogen chloride can cause detachment of radicals.

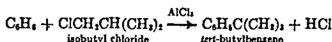
$$2\,\underset{\text{toluene}}{C_6H_5CH_3} \xrightarrow[HCl]{AlCl_3} \underset{\text{xylene}}{C_6H_4(CH_3)_2} + \underset{\text{benzene}}{C_6H_6}$$

Also, a normal alkyl halide yields a secondary or in some cases a tertiary product as the reaction is ordinarily carried out.



$$C_6H_6 + \underset{n\text{-butyl chloride}}{ClCH_2CH_2CH_2CH_3} \xrightarrow{AlCl_3} \underset{sec\text{-butylbenzene}}{C_6H_5CH(CH_3)CH_2CH_3} + HCl$$

The same product is given by *sec*-butyl chloride. Isobutyl and *tert*-butyl chloride both yield *tert*-butyl benzene.



$$C_6H_6 + \underset{\text{isobutyl chloride}}{ClCH_2CH(CH_3)_2} \xrightarrow{AlCl_3} \underset{tert\text{-butylbenzene}}{C_6H_5C(CH_3)_3} + HCl$$

When a second radical enters the ring, usually a mixture of *meta*- and *para*-isomers results; thus toluene yields a mixture of *m*- and *p*-xylene. If the mixture is heated for some time or is allowed to stand a longer time, isomerization of *para*- to *meta*-isomer takes place with the result that usually the product is largely the *meta*-isomer.

Complicated addition compounds are formed involving the hydrocarbon, the alkyl halide, and anhydrous aluminum chloride. The reaction takes place in these complexes.

TABLE 79 | Constants of Some Aromatic Hydrocarbons [a]

NAME	FORMULA	M.P. °C	B.P. °C	SP. GR. 20°/4°	ΔHc KCAL./MOLE gas	ΔHc KCAL./MOLE liquid
Benzene	C_6H_6	5.49	80.07	0.8787	789.08	780.98
Toluene	$C_6H_5CH_3$	−95.18	110.56	0.8665	943.58	934.50
o-Xylene	1,2-$C_6H_4(CH_3)_2$	−25.25	144.18	0.8801		
m-Xylene	1,3-$C_6H_4(CH_3)_2$	−47.87	139.08	0.8641		
p-Xylene	1,4-$C_6H_4(CH_3)_2$	13.27	138.35	0.8610		
Hemellitene	1,2,3-$C_6H_3(CH_3)_3$	−25.47	176.1	0.8947		
Pseudocumene	1,2,4-$C_6H_3(CH_3)_3$	−44.1	169.3	0.8762		
Mesitylene	1,3,5-$C_6H_3(CH_3)_3$	−44.8	164.7	0.8637		
Prehnitene	1,2,3,4-$C_6H_2(CH_3)_4$	−6.5	205.0	0.902		
Isodurene	1,2,3,5-$C_6H_2(CH_3)_4$	−24.2	197.2			
Durene	1,2,4,5-$C_6H_2(CH_3)_4$	79.7	195.4			
Pentamethylbenzene	$C_6H(CH_3)_5$	53	231.4			
Hexamethylbenzene	$C_6(CH_3)_6$	165.3	263.8			
Ethylbenzene	$C_6H_5C_2H_5$	−94.91	136.06	0.8671	1101.13	1091.03
n-Propylbenzene	$C_6H_5(CH_2)_2CH_3$	−99.2	159.2	0.8621	1258.24	1247.19
Cumene	$C_6H_5CH(CH_3)_2$	−96.1	152.4	0.8623		
n-Butylbenzene	$C_6H_5(CH_2)_3CH_3$	−81.2	183.3	0.8604	1415.44	1403.46
p-Cymene	1,4-$CH_3C_6H_4CH(CH_3)_2$	−69.8	176.9	0.8571		
Styrene	$C_6H_5CH{=}CH_2$	−30.6	145.3	0.9067		
Phenylacetylene	$C_6H_5C{\equiv}CH$	−44.8	142.4	0.9300		

[a] Data of first three columns from *Physical Constants of Hydrocarbons*, Vol. III, by Gustav Egloff, Reinhold Publishing, Corp., New York, N. Y., 1946; of last two columns, Circular C461, National Bureau of Standards, Washington, D. C., 1947.

4. *Addition to an olefin.* The reaction of benzene with an olefin takes place in the presence of a suitable catalyst, for example, boron trifluoride, concentrated sulfuric acid, or anhydrous aluminum chloride.

$$C_6H_6 + CH_2{=}CHCH_3 \longrightarrow \underset{\text{isopropylbenzene}}{C_6H_5CH(CH_3)_2}$$

Ethylene is the least reactive olefin. The reaction of benzene and ethylene to form ethyl benzene is one step in the manufacture of styrene, an important industrial chemical. The methods of (3) and (4) are alkylation reactions, for the products are alkylated benzenes.

Nomenclature. The hydrocarbons may be designated by their trivial names, or they may be named as substitution products of benzene, the positions being indicated by number, for example, 1-methyl-4-isopropylbenzene. Substituted hydrocarbons may be named in more than one way; for example, 1,4-$CH_3C_6H_4NO_2$ is 1-methyl-4-nitrobenzene, *p*-nitrotoluene, or 4-nitrotoluene. The numbering starts at the side chain (alkyl group).

Reactions of Benzene Homologs. *Typical substitution reactions.* These hydrocarbons closely resemble benzene in their chemical behavior in that they can be hydrogenated to derivatives of cyclohexane and undergo substitution reactions such as halogenation, sulfonation, nitration, mercuration, and alkylation (Friedel-Crafts reaction).

$$\underset{\text{toluene}}{C_6H_5CH_3} + 3\,H_2 \longrightarrow \underset{\text{methylcyclohexane}}{C_6H_{11}CH_3}$$

$$C_6H_5CH_3 + Cl_2 \xrightarrow[\text{heat}]{\text{light}} \underset{\text{benzyl chloride}}{C_6H_5CH_2Cl} + HCl$$

$$C_6H_5CH_3 + Cl_2 \xrightarrow{FeCl_3} \underset{\substack{\text{chlorotoluenes}\\(o\text{- and }p\text{-})}}{CH_3C_6H_4Cl} + HCl$$

$$C_6H_5CH_3 + H_2SO_4 \longrightarrow \underset{\substack{\text{toluenesulfonic acid}\\(o\text{- and }p\text{-})}}{CH_3C_6H_4SO_3H} + H_2O$$

$$C_6H_5CH_3 + HNO_3 \longrightarrow \underset{\substack{\text{nitrotoluenes}\\(o\text{- and }p\text{-})}}{CH_3C_6H_4NO_2} + H_2O$$

$$C_6H_5CH_3 + (CH_3CO_2)_2Hg \longrightarrow \underset{\substack{\text{tolylmercuric acetate}\\(o\text{- and }p\text{-})}}{CH_3C_6H_4HgOCOCH_3} + CH_3COOH$$

$$C_6H_5CH_3 + CH_3Cl \xrightarrow{AlCl_3} \underset{\text{xylene }(m\text{- and }p\text{-})}{C_6H_4(CH_3)_2} + HCl$$

Ease of substitution. The presence of side chains (alkyl groups joined to the benzene ring) in general facilitates the introduction of other groups, especially halogens, nitro, and sulfo, into the benzene nucleus. Whereas benzene is sulfonated with difficulty by concentrated sulfuric acid at 100°, toluene is slowly sulfonated at that temperature, while mesitylene is sulfonated at room temperature. Toluene is nitrated to the dinitro stage almost as easily as benzene is converted into the mononitro compound.

Halogenation of benzene homologs. At the ordinary temperature the aromatic hydrocarbons do not react rapidly with the halogens. The rate is markedly accelerated by an increase in temperature, by illumination with sunlight or an arc light, or by the

presence of catalysts like anhydrous aluminum or iron halides. Increase in temperature and illumination increases the rate of substitution in the side chain, while many catalysts accelerate substitution in the benzene ring. It is thus possible, in general, to obtain practically complete chlorination or bromination either in the side chain or in the nucleus, depending upon the experimental conditions. Isopropylbenzene is an exception, for it yields ring-substituted derivatives with chlorine when heated. When the halogen enters the side chain, it usually takes a position next to the benzene ring.

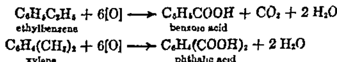
The production of isomers. When toluene undergoes nuclear substitution with halogens, nitric acid, sulfuric acid, or mercury salts, the product is either the *ortho-* or *para-*isomer or else a mixture of the two. The *meta*-isomer is formed in small amount only. It is apparent that the nature of the entering group is not the important factor here but rather the nature of the substituent already attached to the benzene nucleus. The methyl group is said to have an *ortho,para*-directing influence in substitution reactions. Other alkyl groups resemble a methyl group in this respect (p. 437).

Oxidation of side chains. When toluene is boiled with dilute nitric acid, with aqueous dichromic acid, or with alkaline potassium permanganate, the side chain is the main point of attack. The methyl is oxidized to a carboxyl group with the formation of benzoic acid.



$$C_6H_5CH_3 + 3[O] \longrightarrow C_6H_5COOH + H_2O$$

Because of the low solubility of toluene in the aqueous solution, the reaction proceeds so slowly that many hours of heating are required. When a compound is soluble in water, for example, toluic acid, $CH_3C_6H_4COOH$, the oxidation of the side chain takes place with ease. Apparently there is some oxidation of the benzene ring because in general the yields are not quantitative. When ethylbenzene is subjected to oxidation, the product obtained is likewise benzoic acid and propyl- and butylbenzene yield this same product. In general, a side chain, no matter what its size, is oxidized to carboxyl. This reaction serves to distinguish isomeric compounds like ethylbenzene from the xylenes; the former yields a monobasic acid, the latter yield dibasic acids:



$$\underset{\text{ethylbenzene}}{C_6H_5C_2H_5} + 6[O] \longrightarrow \underset{\text{benzoic acid}}{C_6H_5COOH} + CO_2 + 2\,H_2O$$

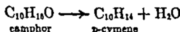
$$\underset{\text{xylene}}{C_6H_4(CH_3)_2} + 6[O] \longrightarrow \underset{\text{phthalic acid}}{C_6H_4(COOH)_2} + 2\,H_2O$$

Toluene, $C_6H_5CH_3$. This is present in coal tar in small amount (*ca.* 1 %) and is separated by means of fractional distillation from benzene and from the higher hydrocarbons. It is obtained from aliphatic hydrocarbons in industry (pp. 55 and 56). It is of importance industrially since it is the starting material for many synthetic drugs and dyes, and also because trinitrotoluene, TNT, is obtained directly from it by nitration. From toluene other important substances are manufactured, among them, benzaldehyde and benzoic acid.

The Xylenes, $C_6H_4(CH_3)_2$. These are present in coal tar in small amount. They are separated from other hydrocarbons by distillation, but cannot easily be separated from each other by this means. The *meta*-isomer can be removed from its mixture with the other two, since it is sulfonated when shaken with cold, concentrated sulfuric acid, while the *ortho-* and *para-*isomers are not. The sulfonated xylene dissolves in the sulfuric acid. When the sulfuric acid is diluted with water and then heated, the *meta*-xylene is regenerated. The *ortho-* and *para-*isomers can then be separated from each other by tedious fractional distillation.

Mesitylene, 1,3,5-$C_6H_3(CH_3)_3$. This is a constituent of coal tar and is best obtained by heating a mixture of acetone and concentrated sulfuric acid (p. 273). It was early assumed, following the announcement of the Kekulé structure of benzene, that mesitylene has the symmetrical structure.

Cymene, 1,4-$C_6H_4CH_3(i\text{-}C_3H_7)$. This occurs in many natural products such as oil of cumin, oil of eucalyptus, oil of nutmeg, and oil of thyme. It is easily prepared by heating camphor with phosphorus pentoxide.



$$\underset{\text{camphor}}{C_{10}H_{16}O} \longrightarrow \underset{p\text{-cymene}}{C_{10}H_{14}} + H_2O$$

Hexamethylbenzene, $C_6(CH_3)_6$. From X-ray investigations of this solid it was shown that the carbon-to-carbon distances in the benzene ring are all alike, and are 1.39 Å. Also, all of the carbon atoms lie in a plane. This feature is inferred from the absence of stereoisomeric form of substituted benzene compounds.

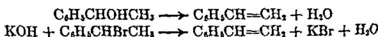
UNSATURATED HYDROCARBONS

Styrene, Phenylethylene, $C_6H_5CH{=}CH_2$ (Styrole). This compound is named from storax (styrax), a gum from the liquid-amber tree. Subjected to steam distillation, the gum yields styrene through the decomposition of the cinnamic acid present. Styrene is also obtained from the sodium salt of cinnamic acid by heating with soda lime, or by slowly distilling the free acid, which undergoes decarboxylation.



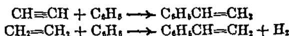
$$C_6H_5CH{=}CHCOOH \longrightarrow C_6H_5CH{=}CH_2 + CO_2$$

The structure of styrene is established by means of this reaction. It can be prepared also by standard methods of forming a double bond, for example, heating methylphenylcarbinol with zinc chloride or heating α-bromoethylbenzene with a base.



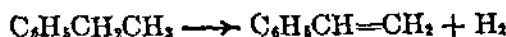
$$C_6H_5CHOHCH_3 \longrightarrow C_6H_5CH{=}CH_2 + H_2O$$
$$KOH + C_6H_5CHBrCH_3 \longrightarrow C_6H_5CH{=}CH_2 + KBr + H_2O$$

Styrene is formed when acetylene is passed into benzene in which anhydrous aluminum chloride is suspended, or when benzene and ethylene are passed through a red hot tube.



$$CH{\equiv}CH + C_6H_6 \longrightarrow C_6H_5CH{=}CH_2$$
$$CH_2{=}CH_2 + C_6H_6 \longrightarrow C_6H_5CH{=}CH_2 + H_2$$

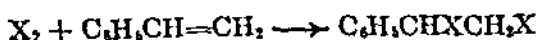
Industrially styrene is produced from benzene and acetylene or by dehydrogenation of ethylbenzene, which is passed over iron oxide or alumina at 1200° F.



$$C_6H_5CH_2CH_3 \longrightarrow C_6H_5CH{=}CH_2 + H_2$$

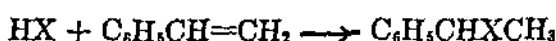
Styrene undergoes polymerization slowly in contact with air, more rapidly if an organic peroxide (benzoyl peroxide, for example) is added. The resulting polystyrene ... made.
RS,
ible
stabilizer is added can be kept for years without polymerizing. Such a stabilizer is an antioxidant, hydroquinone being an example.

Styrene adds chlorine, bromine, or iodine, with formation of α,β-dihaloethylbenzenes. The diiodide decomposes.



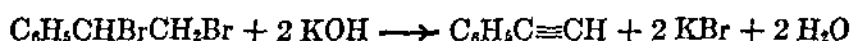
$$X_2 + C_6H_5CH{=}CH_2 \longrightarrow C_6H_5CHXCH_2X$$

Also, it adds, but slowly, hydrogen chloride, bromide, or iodide to form the respective α-halogenoethylbenzene.



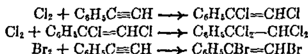
$$HX + C_6H_5CH{=}CH_2 \longrightarrow C_6H_5CHXCH_3$$

Phenylacetylene, $C_6H_5C{\equiv}CH$. This can be prepared by heating α,β-dibromoethylbenzene with a base.



$$C_6H_5CHBrCH_2Br + 2\,KOH \longrightarrow C_6H_5C{\equiv}CH + 2\,KBr + 2\,H_2O$$

Phenylacetylene, like acetylene, rapidly adds chlorine or bromine. Two molecules of chlorine will add.



$$Cl_2 + C_6H_5C{\equiv}CH \longrightarrow C_6H_5CCl{=}CHCl$$
$$Cl_2 + C_6H_5CCl{=}CHCl \longrightarrow C_6H_5CCl_2{-}CHCl_2$$
$$Br_2 + C_6H_5C{\equiv}CH \longrightarrow C_6H_5CBr{=}CHBr$$

Like acetylene, phenylacetylene reacts with sodamide.



$$NaNH_2 + C_6H_5C{\equiv}CH \longrightarrow C_6H_5C{\equiv}CNa + NH_3$$

The sodium salt undergoes the typical reactions, for example, those with water, carbon dioxide, aldehydes, ketones, and reactive alkyl halides.

Identification of Aromatic Hydrocarbons. Heating with a nitrating mixture (a mixture of concentrated nitric and sulfuric acids) serves to distinguish saturated aromatic from saturated aliphatic hydrocarbons. The formation of a liquid having a density greater than unity indicates an aromatic hydrocarbon. In addition, many di- or trinitro compounds are solid.

Saturated aromatic may be distinguished from unsaturated aliphatic hydrocarbons with aqueous permanganate or with a solution of bromine in carbon tetrachloride. The unsaturated hydrocarbon reacts rapidly with either, whereas the saturated aromatic one reacts only slowly, if at all, at ordinary temperature.

PROBLEMS

1. Write the structural formula of an aromatic hydrocarbon having just the indicated number of theoretically possible mononitro derivatives in which the nitro group is directly attached to the benzene ring:

a) C_9H_{12}, one
b) C_9H_{12}, two
c) C_9H_{12}, three
d) $C_{10}H_{12}$, two
e) $C_{10}H_{12}$, three
f) $C_{10}H_{14}$, four
g) $C_{10}H_{14}$, one
h) $C_{10}H_{14}$, two
i) $C_{10}H_{14}$, three
j) $C_{10}H_{14}$, four

2. Write the structural formula of the aromatic hydrocarbon having the following formula and just the indicated number of theoretically possible, structurally isomeric monochloro derivatives.

a) $C_{10}H_{14}$, three
b) $C_{10}H_{14}$, four
c) $C_{10}H_{14}$, five
d) $C_{10}H_{14}$, six
e) $C_{10}H_{14}$, seven
f) $C_{10}H_{14}$, eight
g) $C_{10}H_{10}$, three
h) $C_{10}H_{10}$, four
i) $C_{10}H_{10}$, five
j) $C_{10}H_{10}$, six
k) $C_{10}H_{10}$, seven
l) $C_{10}H_{10}$, eight

3. A mononitro derivative, *A*, of an aromatic hydrocarbon (nitro group on the ring) has just four theoretically possible, structurally isomeric monobromo derivatives, *B*, *C*, *D*, and *E*. Write a structural formula for *A*, whose empirical formula is:

a) $C_8H_7O_2N$
b) $C_9H_9O_2N$
c) $C_{10}H_{11}O_2N$
d) $C_{11}H_{13}O_2N$
e) $C_8H_9O_2N$
f) $C_9H_{11}O_2N$
g) $C_{10}H_{13}O_2N$
h) $C_{11}H_{15}O_2N$
i) $C_{12}H_{15}O_2N$
j) $C_{13}H_{17}O_2N$
k) $C_{14}H_{19}O_2N$
l) $C_{15}H_{21}O_2N$
m) $C_{12}H_{17}O_2N$
n) $C_{13}H_{19}O_2N$
o) $C_{14}H_{21}O_2N$
p) $C_{15}H_{23}O_2N$

4. Calculate from bond energies and resonance energies ΔH for the gas phase addition reaction to benzene of:

a) bromine (one mole, two moles, and three moles)
b) chlorine (one mole, two moles, and three moles)
c) iodine (one mole, two moles, and three moles)
d) fluorine (one mole, two moles, and three moles)
e) hydrogen bromide (one mole, two moles, and three moles)
f) hydrogen chloride (one mole, two moles, and three moles)
g) hydrogen iodide (one mole, two moles, and three moles)

5. Write the structure of the aromatic hydrocarbon that you predict to be the *initial* main product when benzene in the presence of anhydrous aluminum chloride reacts with:

a) *n*-propyl chloride
b) isopropyl chloride
c) isobutyl bromide
d) *tert*-butyl bromide
e) *n*-amyl chloride
f) 2-chloropentane
g) 1-chloro-2-methylbutane
h) 2-chloro-2-methylbutane
i) 3-chloro-2-methylbutane
j) 2-chloro-3-methylpentane

6. Outline the steps in a practical laboratory preparation of the following, from compounds of fewer carbon atoms.

a) *n*-amylbenzene
b) isohexylbenzene
c) *sec*-butylbenzene
d) 2-methyl-2-phenylbenzene
e) *p*-allyltoluene
f) *p*-*n*-propyltoluene
g) *p*-*tert*-butyltoluene
h) *m*-*tert*-butyltoluene
i) *p*-allyl-*n*-propylbenzene
j) 4-*p*-tolyl-1-butene
k) 1-phenyl-1-butyne
l) 1-*p*-tolyl-1-pentyne

7. An aromatic hydrocarbon, *A*, on oxidation is converted into a dibasic acid, *B*, $C_6H_4(COOH)_2$. Write the structure of *A*, whose formula is given below and of which the number of mononitro derivatives (nitro group attached to ring carbon) is indicated.

a) C_8H_{10}, one
b) C_8H_{10}, two
c) $C_{10}H_{14}$, one
d) $C_{10}H_{14}$, two (all possibilities)

8. Describe a convenient chemical test (reagent, conditions, solvent, and readily detectable change) that serves to distinguish between:

a) toluene and methylcyclohexane
b) *m*-xylene and *p*-xylene
c) styrene and ethylbenzene
d) styrene and phenylacetylene
e) ethylbenzene and phenylacetylene
f) benzene and cyclohexene
g) toluene and 1-methyl-1,3-cyclohexadiene
h) *p*-xylene and 1,4-dimethylcyclohexane

CHAPTER 28

Orienting Influence During Substitution in the Benzene Ring

***meta*-Orientation and *ortho,para*-Orientation.** In the preceding chapter it was noted that when toluene is halogenated, sulfonated, or nitrated, the entering substituent takes a position that is *ortho* or *para* to the methyl group already present and has little tendency to go to the *meta*-position. A small amount of the *meta*-isomer is formed, however. When benzene is nitrated with a powerful nitrating mixture, or sulfonated with an excess of fuming sulfuric acid, the dinitrobenzene and the disulfonic acid formed are mainly the *meta*-isomers. Moreover, when mononitrobenzene and benzenesulfonic acid undergo other substitutions, the principal products are the *meta*-isomers. The methyl group therefore directs other entering substituents mainly to the *ortho*- and *para*-positions, while the nitro and the sulfonic acid groups direct them mainly to the *meta*-position. When any benzene derivative undergoes substitution, it is found in general that the nature of the reaction product, *i.e.*, whether it is chiefly the *meta*-isomer or a mixture of the *ortho*- and *para*-isomers, is largely determined by the group already attached to the benzene ring. The nature of the entering group, the temperature, the solvent, or the catalyst may also influence, although usually to a much less extent, the proportion of isomers formed.

On the basis of the products formed on substitution, the groups that may be attached to the benzene ring fall into two classes, *viz.*, (1) those that send the second substituent mainly to the *meta*-position, and (2) those that send it mainly to the *ortho*-position or to the *para*-position or to both. The former are called the *meta*-orienting groups, and the latter the *ortho,para*-orienting groups. Inasmuch as two of the five possible positions are *meta*, it is customary to take 40 per cent, as the dividing line, *i.e.*, when more than 40 per cent of the reaction product is the *meta*-isomer, the group is called *meta*-, and when less than 40 per cent, *ortho,para*-orienting.

Table 80 lists the products formed when various monosubstituted benzenes, C_6H_5Y, are converted into mononitro compounds, $C_6H_4YNO_2$. It is evident that there is a gradation in the orienting influence of the different substituents from those like nitro that send the second substituent almost completely to the *meta*-position, to those like hydroxyl that send it entirely to the *ortho*-

and *para*-positions Some, like dichloromethyl, $CHCl_2$, are borderline cases and possess neither *meta*- nor *ortho,para*-orientation. The order of orienting influence in Table 80 is true of nitration. The order for other substitution reactions, for example bromination, is generally similar, but with variations.

TABLE 80 | **Isomers Formed by the Nitration of C_6H_5Y**

NAME OF COMPOUND	SUBSTITUENT Y	PERCENTAGE OF			
		ortho	*para*	*ortho* and *para*	*meta*
Phenyltrimethylammonium nitrate	$N(CH_3)_3^+$	0	0	0	100
Nitrobenzene	NO_2	6.4	0.25	6.7	93.2
Benzonitrile	CN			11.5 *	88.5
Benzoic acid	COOH	18.5	1.3	19.8	80.2
Benzaldehyde	CHO			21.4 *	78.6
Benzenesulfonic acid	SO_3H	21.1	6.5	27.6	72.4
Ethyl benzoate	$COOC_2H_5$	28.3	3.3	31.6	68.4
Benzotrichloride	CCl_3	6.8	28.7	35.5	64.5
Acetophenone	$COCH_3$	45		45	55
Aniline sulfate	NH_3SO_4H	2.1	51.3	53.4	46.6
Benzal chloride	$CHCl_2$	23.3	42.9	66.2	33.8
Benzyl chloride	CH_2Cl	41	47.4	88.4	11.6
Toluene	CH_3	58.8	36.8	95.6	4.4
Acetanilide	$NHCOCH_3$	19.4	78.5	97.9	2.1
Iodobenzene	I	41.1	58.7	99.8	Trace
Bromobenzene	Br	37.6	62.4	100.0	"
Chlorobenzene	Cl	30.1	69.9	100.0	"
Fluorobenzene	F	12.4	87.6	100.0	"
Phenol	OH	50–55	50–45	100.0	

* By difference.

The amino and alkylated amino groups, such as NH_2, NHR, and NR_2, are not included in this list, because in the presence of strong acids they are converted respectively into NH_3X, NH_2RX, and NHR_2X, which are *meta*-orienting. In other reactions such as halogenation, the amino, NH_2, monoalkylamino, NHR, and dialkylamino group, NR_2 are strongly *ortho,para*-orienting groups and stand very close to the hydroxyl group.

Groups are classified as (1) *meta*-orienting or (2) *ortho,para*-orienting on the 40 per cent basis already mentioned. In the following lists radicals are in general in the order of decreasing orientation; R in general represents an alkyl radical although in most cases R can be also an unsaturated or an aromatic radical.

1. *Meta:* $\overset{+}{N}R_3$, $\overset{+}{P}R_3$, NO_2, CN, SO_2OH, SO_2Cl, SO_2OR, SO_2R, SO_2NH_2, CHO, COR, COOH, COCl, COOR, $CONH_2$, CCl_3, $\overset{+}{N}HR_2$, $\overset{+}{N}H_2R$, $\overset{+}{N}H_3$, N=N—R, N_2^+.

2. *Ortho,para:* NR_2, NHR, $NHCOCH_3$, OH, OR, OCOR, SH, SR, CH_3, CH_2R, CH_2Cl, C_6H_5, F, Cl, Br, I.

It is important to note that usually a positively charged group is strongly *meta*-orienting, but that $\overset{+}{N}HR_2$, $\overset{+}{N}H_2R$, and $\overset{+}{N}H_3$ are not nearly so strongly *meta*-orienting. This difference is explained by the reversibility of the reaction between an acid and a weak aromatic base, for example, $C_6H_5NR_2$, C_6H_5NHR, and $C_6H_5NH_2$. The presence of even a very small amount of the very reactive free amino or substituted amino compound would lead to the formation of some *ortho-* and *para*-substitution products.

The proportion of *ortho-*, *meta-*, and *para*-isomers formed during a nitration, or some other substitution, often changes as a change is made in conditions, for example, temperature, solvent, or catalyst. Moreover, the proportion of isomers attending sulfonation may be different from that attending nitration, and so on. Usually the orientation characteristic of nitration holds for other substitutions, but the ratio of *ortho* to *para* may vary markedly, depending on the reaction and/or the conditions. These statements are illustrated by the data of Table 81.

TABLE 81 | Effect of Entering Group and of Conditions

COMPOUND	REACTION	CONDITION	PERCENTAGE OF		
			ortho	*para*	*meta*
Toluene	bromination	dark	42	58 [a]	0
	bromination	dark, $FeCl_3$	37	63	0
	nitration	−30°	57	39	4
	nitration	60°	60	35	5
	sulfonation	0°	43	53	4
	sulfonation	100°	13	79	8
Bromobenzene	bromination	55°, $AlCl_3$	8	62	30
	bromination	55°, $FeCl_3$	13	85	2
	chlorination	75°, $AlCl_3$	30	65	5
	chlorination	75°, $FeCl_3$	42	51	7
	nitration	0°	38	62	0
	sulfonation		0	100	0
Chlorobenzene	bromination	130°	17.5	81.3	1.2
	bromination	55°, $FeBr_3$	11	87.5	1.5
	chlorination	75°, $AlCl_3$	30	66	5
	chlorination	75°, $FeCl_3$	40	55	5
Acetanilide	nitration	−20°, 80% HNO_3	41	59	0
	nitration	−20°, 90% HNO_3	23.5	75 5	0
	nitration	−20°, H_2SO_4	4.5	95.5	0
	nitration	−25°, acetyl nitrate, CCl_4	76	20	4

[a] Benzylbromide, 45 per cent of total products.

Orientation and Electronegative Character of Radicals. The *meta*-orienting radicals in general are those characteristic of strong acids (Table 16,

p. 35), that is, they are strongly electronegative radicals *in comparison to* the hydrogen atom that they may be regarded as replacing. (It is difficult to classify the positively charged radicals, like $(CH_3)_3N^+$, on the basis of the acid strengths of the respective hydroxy compounds, because such a radical can exist only as a component of a salt.) Thus when a strongly electronegative radical is attached to a carbon atom, for example, a carbon atom of the benzene ring, the electron pair forming the bond is strongly attracted by the radical. There is a pronounced dipole moment in the bond and it points away from the carbon atom. It would be expected that a positive pole, for example, the trimethylammonium group, $(CH_3)_3N^+$, would exert an exceptionally strong pull on the electron pair, and thus cause the bond joining it to carbon to exhibit a strong dipole moment.

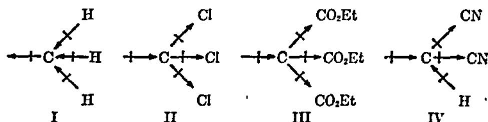
The *ortho,para*-orienting radicals in general are those characteristic of weak acids (Table 16), that is, they are less strongly electronegative than nitro, for example, chloro and bromo, or they are even electropositive (CH_3), compared to a hydrogen atom. Thus the permanent dipole moment in the bond between one of these radicals and a carbon atom of the benzene ring would be expected to be smaller than in a nitro compound if it is pointing towards a weaker electronegative radical or even to point towards the ring when the radical is electropositive in nature.

TABLE 82 | **Modification of Orienting Power**

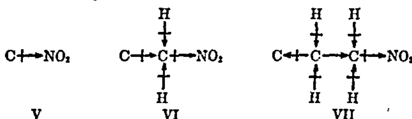
Radical	CH_3	CH_2Cl	$CHCl_2$	CCl_3
% meta	4.4	11.6	33.8	61.7
Radical	CH_3	CH_2CO_2Et	$CH(CO_2Et)_2$	$C(CO_2Et)_3$
% meta	4.4	12	25	56
Radical	CH_3	CH_2CN	$CH(CN)_2$	
% meta	4.4	12.7	68	
Radical	NO_2	CH_2NO_2	$CH_2CH_2NO_2$	
% meta	93	48	13	

Modification of Orienting Influence. It is evident from the data of Table 82 that the *ortho,para*-orientation of the methyl group gradually changes to *meta*-orientation as chlorine replaces hydrogen, for trichloromethyl, CCl_3 is definitely *meta*-orienting. The same is true of the carbethoxy group, CO_2Et, and cyano group, CN. In methyl chloride, CH_3—Cl, ethyl acetate, CH_3—CO_2Et, and methyl cyanide, CH_3—CN, the dipole moment in the bond joining the radical to carbon points away from the methyl carbon atom (Table 16). The replacement of hydrogen atoms of the *methyl* group by three Cl, three CO_2Et, or two CN groups changes methyl from electropositive to electronegative, through the operation of the inductive effect. This is shown schematically by I, II, III, and IV, respectively, in which the relative strengths of the dipoles are indicated by the distance from head to crossbar of the arrows. The observation that IV is more strongly *meta*-orienting than II is a good argument for this

point of view because the cyano group is more electronegative than the chloro group as shown by the greater dipole moment of a cyano compound in comparison to a corresponding chloro compound (Table 16).



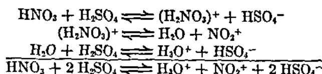
The strong *meta*-orientation of the nitro group is diminished by placing carbon atoms between it and the benzene ring (Table 82). The strong inductive effect of the nitro group is partially neutralized by the effect of dipoles of opposite sign in the C—H bonds. Also, the resonance effect (p. 36) does not operate when the nitro group is not directly attached to ring carbon. The diminishing of the inductive effect is shown schematically by V, VI, and VII.



It will be recalled that a similar explanation accounts for the fact that removal of a chloro substituent away from the carboxyl group results in a decrease of acid strength (p. 205).

Relative Rates in Substitution. Compared to benzene, a *meta*-orienting substituent decreases the rate of nitration and an *ortho,para*-orienting substituent, except a halogen, increases the rate. In general, the same relationships hold for other substitutions. Although the halogen atoms are an apparent exception, it is noted that they operate like other electronegative radicals in diminishing the rate. Among the *meta*-orienting substituents, those having the strongest influence diminish the rate the most, and among the *ortho,para*-orienting ones, those having the strongest influence increase the rate the most. The rates in general follow this order: OH, NH_2 > OR, OCOR, NHCOR > CH_3 > H > X > COOH > SO_3H > NO_2.

Theory of Substitution. The substituting reagents, in particular chlorine, bromine, nitric acid, and sulfuric acid are electrophilic, and react fastest at the place where electrons are available. The reaction is believed to involve the formation of a positively charged ion, perhaps as one of the reactants, but in any event as one of the intermediates. The evidence for this in the case of nitration is rather convincing. It is known that the rate of nitration of benzene with a nitric-sulfuric acid nitration mixture rises as the concentration of sulfuric acid in the mixture increases. Measurements of the freezing point lowering of 100 per cent sulfuric acid caused by the addition of anhydrous (100%) nitric acid indicate the formation of four discrete particles per molecule of nitric acid added (van't Hoff i factor = 4). This shows that the following reactions have taken place, and that the extent of any reverse reaction is slight.



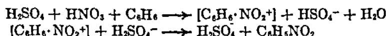
$$
\begin{aligned}
HNO_3 + H_2SO_4 &\rightleftharpoons (H_2NO_3)^+ + HSO_4^- \\
(H_2NO_3)^+ &\rightleftharpoons H_2O + NO_2^+ \\
H_2O + H_2SO_4 &\rightleftharpoons H_3O^+ + HSO_4^- \\
\hline
HNO_3 + 2\,H_2SO_4 &\rightleftharpoons H_3O^+ + NO_2^+ + 2\,HSO_4^-
\end{aligned}
$$

In ordinary concentrated nitric and sulfuric acid mixture the concentration of positive nitronium ion is very much lower than in the anhydrous acid mixture because of the presence of water. Water acts not only to cause a reversal of the second equation, but also it competes with nitric acid for the proton of sulfuric acid.

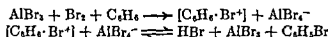


$$H_2O + H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^-$$

The first step in the reaction of benzene with a substituting reagent involves the formation of a positively charged coordination complex, similar to the reaction of benzene with silver ion (p. 423). If the first step is the formation of a complex, it would seem reasonable for reaction to proceed fastest where electrons are available. Thus in a substituted benzene the effect of the substituent on electron availability becomes important. The intermediate positively charged ion loses a proton to some proton acceptor present, as, for example, bisulfate ion in the sulfonation mixture, or bromoaluminate ion in the bromination mixture, to yield the final product.



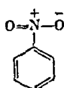
$$
\begin{aligned}
H_2SO_4 + HNO_3 + C_6H_6 &\longrightarrow [C_6H_6{\cdot}NO_2^+] + HSO_4^- + H_2O \\
[C_6H_6{\cdot}NO_2^+] + H_2SO_4^- &\longrightarrow H_2SO_4 + C_6H_5NO_2
\end{aligned}
$$



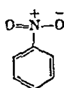
$$
\begin{aligned}
AlBr_3 + Br_2 + C_6H_6 &\longrightarrow [C_6H_6{\cdot}Br^+] + AlBr_4^- \\
[C_6H_6{\cdot}Br^+] + AlBr_4^- &\rightleftharpoons HBr + AlBr_3 + C_6H_5Br
\end{aligned}
$$

The catalytic effect of anhydrous aluminum bromide may be due in part to its tendency to form the stable negative bromoaluminate ion, $AlBr_4^-$. Anhydrous ferric bromide forms the similar bromoferrate ion, $FeBr_4^-$. There are other hypotheses of the substitution reaction. Advantages of the hypothesis based on an intermediate positive ion are: (1) differentiation from a free radical mechanism such as the one characteristic of halogenations accelerated by illumination; (2) correlation with additions to olefinic double bonds, known to be *trans*-additions (p. 315); (3) application to benzene substitution and to orientation during substitution.

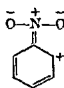
The effect of the nitro group in decreasing the reactivity of the benzene ring is explained as a drain of electrons away from the benzene ring, owing to the strong permanent dipole of the nitro group, V, page 35. In addition to this drain of electrons by induction, there is another drain of electrons by resonance, and this is now generally regarded as the cause of the orienting effect of the nitro group.



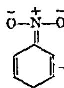
VIII



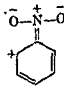
IX



X



XI

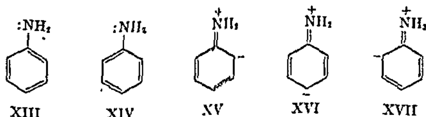


XII

The Kekulé forms, VIII and IX (including also VIII′ and IX′, not shown, having the negative charge on the other oxygen atom) contribute most to the overall structure of nitrobenzene, but X, XI, and XII, although less important from the standpoint of stability, are more important from the standpoint of reactivity. In order for each

oxygen atom to carry a formal negative charge, an electron pair of the carbon-to-carbon double bond must swing over towards the nitrogen atom, to make the carbon-to-nitrogen double bond. This leaves only six electrons in the valence shell of the *ortho*-carbon atom and this puts a formal positive charge on this carbon atom. This charge can resonate among the *para*- and the two *ortho*-carbon atoms. It is seen that the *para*- and the two *ortho*-positions suffer a still further drain of electrons as a result of the resonance. Thus the *para*- and two *ortho*-carbon atoms are more deficient in electrons than the *meta*-carbon atoms, which are not affected by the resonance. An attacking electrophilic reagent, therefore, reacts more slowly with nitrobenzene than with benzene and faster at *meta*-positions than at the *ortho*- and *para*-positions. This is because the electrophilic reagent reacts most rapidly at those positions where electron densities are the highest, namely, the *meta*-positions. This is one explanation of why nitration of nitrobenzene gives mainly *m*-dinitrobenzene, bromination gives mainly *m*-bromonitrobenzene, etc. It will be noted that, in the majority of the *meta*-orienting groups mentioned on page 436, the atom attached to ring carbon also is attached to some other atom by a multiple bond. It is easy to see that the resonance forms of these molecules put positive formal charges on the *ortho*- and *para*-carbon atoms. Summarizing the effect of the permanent dipole in draining electrons from the ring, the inductive effect acts in the same direction as the resonance effect, which also removes electrons from the ring and which, in addition, is responsible for the *meta*-orientation of the nitro group. Thus, a lower rate of reaction and *meta*-orientation go together.

The effect of the amino group in increasing the reactivity of the benzene ring is explained as resulting from increased availability of electrons arising from resonance involving the forms, XV, XVI, and XVII. This effect is so pronounced that it completely outweighs any inductive effect operating in the reverse direction.



The two Kekulé *forms*, XIII and XIV, contribute most to the overall structure of the molecule of aniline, but XV, XVI, and XVII also contribute, even though the [illegible] carries the formal positive charge [illegible]

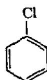
[illegible]

densities at the *ortho*- and *para*-carbon atoms are higher than at the *meta*-carbon atoms, and thus these are the positions attacked by an eletrophilic reagent. When chlorine or bromine reacts, the product is a mixture of the corresponding *ortho*- and *para*-halogenoanilines, or even higher substitution products. Nitric acid acts differently, but this is because the amino group cannot exist as such in an excess of strong acid owing to salt formation. However, modified amino groups that do not readily form salts because of their weakly basic character, such as the acetylamino group, $NHCOCH_3$, promote rapid nitration with nitric acid and lead to the formation of *o*- and *para*-

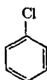
acetanilides. The resonance effect is responsible for the *ortho,para*-orientation of the amino group. Thus an increased rate of reaction and *ortho,para*-orientation go together.

Inspection of the *ortho,para*-orienting groups listed on page 437 shows that in most of them the atom attached to ring carbon has two or more unshared electrons. These can promote *ortho,para*-orientation in the same way those on the nitrogen atom of the amino group do. The hydroxyl group deserves mention along with the amino group because it also has a strongly activating influence and promotes *ortho,para*-orientation to the almost complete exclusion of *meta*.

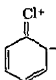
Halogeno radicals are unusual in promoting *ortho,para*-orientation, and yet diminishing the substitution rate, in comparison to benzene. The lowered rate is due to the fact that the moderately strong dipole in the carbon-to-halogen bond points away from the carbon atom. The *ortho,para*-orientation is due to the presence of unshared electrons on the halogen atom, because these can swing in between the halogen and carbon atoms to produce a double bond, as already mentioned in the case of the amino group. This places negative formal charges on *para*- and *ortho*-carbon atoms. The structure of chlorobenzene has, in addition to the two Kekulé forms, XVIII and XIX, three other forms, XX, XXI, and XXII (see p. 451).



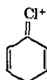
XVIII



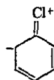
XIX



XX



XXI

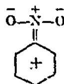


XXII

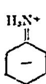
Since second row and higher elements do not form double bonds as easily as do first row elements, XX, XXI, and XXII make a smaller contribution to the structure of *chlorobenzene than* XV, XVI, *and* XVII *do to that of aniline*. The deactivating influence of the inductive effect in this case is so important, relative to the activating influence of the resonance effect, that the rate is lower, even though the chloro group promotes *ortho,para*-substitution. The other halogeno groups produce much the same effect as chloro.

Two generalizations are seen to hold for substitution by electrophilic reagents The rate of substitution is determined by the inductive effect of the substituent already attached to the benzene ring, and the orientation is governed by the resonance effect.

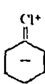
The concept of resonance forms that place either positive or negative formal charges on *ortho*- and *para*-carbon atoms of the benzene ring is believed to be quite well established. Use will be made of this concept from time to time in these pages. A symbol that expresses these states is illustrated by XXIII, XXIV, and XXV, which represent, respectively, X to XII, XV to XVII, and XX to XXII.



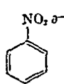
XXIII



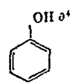
XXIV



XXV



XXVI



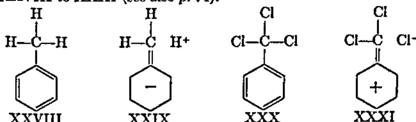
XXVII

Each of these is to be considered equivalent to the three corresponding resonance forms having the respective charges on the *para*- and two *ortho*-carbon atoms.

A consideration of the relative contributions of the different electronic forms to the overall structure indicates that the forms represented by XXIII, XXIV, and XXV put considerably less than a complete charge on the benzene ring. Since this charge is divided among three positions, the charge on either one is a small fraction of unit charge. It is customary to represent these small part charges by deltas, for example, XXVI for an unreactive *para*-position of nitrobenzene and XXVII for a reactive *para*-position of phenol.

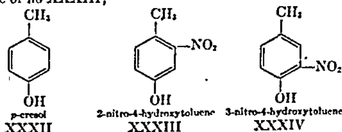
An important effect of resonance is increased polarizability (p. 28). As the electron cloud about a molecule becomes more diffuse it is more subject to distortion by the electrical fields of other molecules. This leads to an enhancement of the part charges and thus to increased reactivity, when in the neighborhood of a polar molecule.

Hyperconjugation (No-Bond Resonance). There is another type of resonance that is postulated in order to account for the *ortho,para*-orientation of the methyl and other alkyl radicals and for the *meta*-orientation of the trichloromethyl and other similar groups. This postulate recalls the resonance forms of propargyl chloride, in one of which there is ionization to produce a negatively charged chlorine ion and a positively charged carbonium ion (p. 116). The nature of hyperconjugation is shown by formulas XXVIII to XXXI (see also p. 74).



Thus the effect of the permanent dipoles of the methyl and trichloromethyl groups are reinforced by the resonance effects.

Directive Power of Groups. When substitution takes place on the ring of an aromatic compound to which two radicals are attached, the product formed depends upon the nature of the two radicals and their relative positions. There may be support or opposition between the orienting influences of the two groups. Two simple cases are the nitration of *p*-cresol, XXXII, which yields essentially 100 per cent of XXXIV and little or no XXXIII;

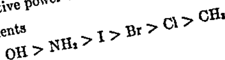


and of *p*-chlorotoluene, XXXV, which yields 58 per cent of XXXVI and 42 per cent of XXXVII.



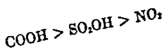
Here it is evident that the hydroxyl group promotes substitution much more than does the methyl group, while the methyl group promotes only a little more than does the chloro. However, when the nitration of *o*- and *m*-chlorotoluenes is taken into account, the opposite conclusion is drawn. From numerous experiments Holleman has deduced an order of diminishing velocities in the introduction of a third group into C_6H_4XY. This order may be considered to represent the directive power of substituents. On it and other data are based the rules governing substitution in the benzene ring. The directive power of groups stands in the following order:

for *o,p*-directing substituents



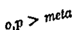
$$OH > NH_2 > I > Br > Cl > CH_3$$

for *m*-directing substituents



$$COOH > SO_2OH > NO_2$$

and for substituents in general



$$o,p > meta$$

PROBLEMS

1. Indicate by graphic formulas the principal product (or products) to be expected from ring monochlorination of the following:

- *a*) fluorobenzene
- *b*) ethylbenzene
- *c*) methyl benzoate
- *d*) methyl phenyl ether
- *e*) N,N-dimethyl aniline
- *f*) phenyl mercaptan
- *g*) phenyl cyanide
- *h*) ethyl phenyl ether
- *i*) ethyl phenyl ketone
- *j*) chlorobenzene
- *k*) benzoyl chloride
- *l*) benzamide
- *m*) phenyl acetate
- *n*) benzenesulfonyl amide

2. Ditto:

- *a*) 1,2-$C_6H_4Cl_2$
- *b*) 1,3-$C_6H_4Cl_2$
- *c*) 1,4-$C_6H_4Cl_2$
- *d*) 1,2-$C_6H_4(COOCH_3)Cl$
- *e*) 1,3-$C_6H_4(COOCH_3)Cl$
- *f*) 1,4-$C_6H_4(OCH_3)Cl$
- *g*) 1,2-$C_6H_4(OCH_3)Cl$
- *h*) 1,3-$C_6H_4(OCH_3)Cl$
- *i*) 1,4-$C_6H_4(OCH_3)Cl$
- *j*) 1,2-$C_6H_4(NHCOC_6H_5)Cl$
- *k*) 1,3-$C_6H_4(NHCOC_6H_5)Cl$
- *l*) 1,4-$C_6H_4(NHCOC_6H_5)Cl$
- *m*) 1,2-$C_6H_4(CN)Cl$
- *n*) 1,3-$C_6H_4(CN)Cl$
- *o*) 1,4-$C_6H_4(CN)Cl$
- *p*) 1,2-$C_6H_4(OCOCH_3)Cl$
- *q*) 1,3-$C_6H_4(OCOCH_3)Cl$
- *r*) 1,4-$C_6H_4(OCOCH_3)Cl$
- *s*) 1,3-$C_6H_4(NO_2)Br$
- *t*) 1,4-$C_6H_4(NO_2)Br$

3. Indicate by graphic formulas the principal product (or products) to be expected from ring mononitration of the following:

- *a*) benzaldehyde
- *b*) *n*-butylbenzene
- *c*) ethyl benzoate
- *d*) *n*-propyl phenyl ketone
- *e*) bromobenzene
- *f*) benzotrichloride
- *g*) methyl phenyl sulfide
- *h*) benzoyl bromide
- *i*) methyl phenyl ether
- *j*) methyl benzoate
- *k*) trimethylphenylammonium nitrate
- *l*) phenyl propionate
- *m*) acetanilide
- *n*) biphenyl
- *o*) benzenesulfonyl chloride
- *p*) *p*-cyanotoluene

4. Ditto:

a) 1,2-$C_6H_4(CH_3)NO_2$
b) 1,3-$C_6H_4(CH_3)NO_2$
c) 1,4-$C_6H_4(CH_3)NO_2$
d) 1,2-$C_6H_4(CH_3)OH$
e) 1,3-$C_6H_4(CH_3)OH$
f) 1,4-$C_6H_4(CH_3)OH$
g) 1,2-$C_6H_4(COOH)CN$
h) 1,3-$C_6H_4(COOH)CN$
i) 1,4-$C_6H_4(COOH)CN$
j) 1,2-$C_6H_4(CHO)OCOCH_3$
k) 1,3 $C_6H_4(CHO)OCOCH_3$
l) 1,4 $C_6H_4(CHO)OCOCH_3$
m) 1,2 $C_6H_4(C_2H_5)NHCOCH_3$
n) 1,3 $C_6H_4(C_2H_5)NHCOCH_3$
o) 1,4 $C_6H_4(COOH)NO_2$
p) 1,2 $C_6H_4(COOH)NO_2$
q) 1,3 $C_6H_4(COOH)NO_2$
r) 1,4 $C_6H_4(CH_3)COOH$
s) 1,3 $C_6H_4(CH_3)COOH$
t) 1,4 $C_6H_4(CH_3)COOH$

5. Indicate the sequence of operations to be followed in preparing the following from benzene, assuming that a para-isomer can be obtained pure from a mixture consisting mainly (?) of the ortho- and para-isomers:

a) 1,3-$C_6H_4(NO_2)Cl$
b) 1,4-$C_6H_4(NO_2)Cl$
c) 1,3-$C_6H_4(SO_3H)Br$
d) 1,4-$C_6H_4(SO_3H)Br$
e) 1,4-$C_6H_4(CH_3)SO_3H$
f) 1,4-$C_6H_4(CH_3)NO_2$
g) 1,3-$C_6H_4(COOH)NO_2$
h) 1,4-$C_6H_4(COOH)NO_2$
i) 1,4-$C_6H_4(COOH)Br$
j) 1,3-$C_6H_4(COOH)Cl$
k) 1,2,4-$C_6H_3C_6H_5(NO_2)_2$
l) 1,2,4-$C_6H_3(CH_3)(Cl)NO_2$
m) 1,2,4-$C_6H_3(CH_3)(Br)SO_3H$
n) 1,2,4-$C_6H_3(Br)(SO_3H)NO_2$
o) 1,2,4-$C_6H_3(Br)_2SO_3H$
p) 1,2,4-$C_6H_3COOH(Br)_2$
q) 1,3,4-$C_6H_3(CH_3)(Br)NO_2$
r) 1,2,4-$C_6H_3(COOH)(NO_2)Br$
s) 1,3,4-$C_6H_3(Br)_2NO_2$
t) 1,2,4-$C_6H_3(COOH)(Br)Cl$

attached to the benzene ring, the more difficult is the introduction of subsequent radicals. This is because a halogen atom, although it is *ortho,para*-orienting, diminishes the rate of substitution, owing to its inductive effect (p. 442). Also, two halogen atoms, *ortho* or *para* to each other, act in opposition.

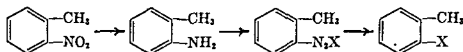
Iodine alone does not cause substitution of hydrocarbons, but when a reactive hydrocarbon is heated with iodine and a suitable oxidizing agent (for example, iodic acid, nitric acid, or persulfate), an iodo derivative is formed.



$$5\,C_6H_5C_2H_5 + 2\,I_2 + HIO_3 \longrightarrow 5\,IC_6H_4C_2H_5 + 3\,H_2O$$

Benzene requires heating to 200° in a sealed tube.

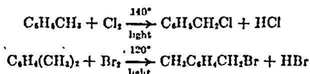
2. *From diazonium salts.* This very important method is described more fully in Chapter 32. The possibilities are shown for *ortho*-halogenotoluenes.



It is possible to put fluorine, chlorine, bromine, or iodine into a position on the ring previously occupied by an amino group. Since the amino compounds are obtained by reduction of nitro compounds, many of which can be obtained pure, either as commercial products or by suitable methods and, since it is not always easy to effect a satisfactory separation of both isomeric halogen compounds from an *ortho,para*-mixture, the method is used extensively.

3. *From phenols (aryl hydroxy compounds).* These do not react with the hydrogen halides and give only poor yields with the phosphorus halides.

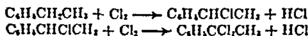
Preparation of Aralkyl Derivatives (Derivatives with a Functional Group on a Side Chain). As in the aliphatic series (Chap 8) these may be obtained from the corresponding alcohol with a suitable reagent (hydrogen halide, phosphorus halide, thionyl chloride, etc.) or by direct substitution. Substitution in the side chain is promoted by heating (for brominations, above 120°) and by illumination with sunlight or with light rich in the violet or ultraviolet part of the spectrum. Phosphorus halides are good "carriers" for side chain halogenation. Side chain halogenation proceeds *via* a free radical mechanism and ring substitution *via* an ionic mechanism. Reaction proceeds without complication at methyl groups, except that dihalogenation also may take place.



$$C_6H_5CH_3 + Cl_2 \xrightarrow[\text{light}]{140°} C_6H_5CH_2Cl + HCl$$

$$C_6H_4(CH_3)_2 + Br_2 \xrightarrow[\text{light}]{120°} CH_3C_6H_4CH_2Br + HBr$$

With a longer side chain, substitution under illumination may proceed at the α-position if the temperature is about 0°. For example, ethylbenzene even gives, with 2 moles of halogen, α,α-dichloro and α,α-dibromobenzene.



$$C_6H_5CH_2CH_3 + Cl_2 \longrightarrow C_6H_5CHClCH_3 + HCl$$

$$C_6H_5CHClCH_3 + Cl_2 \longrightarrow C_6H_5CCl_2CH_3 + HCl$$

At higher temperatures chlorine may enter the β-position. Hydrocarbons with longer side chains give more complicated mixtures.

Separation of Reaction Mixtures. When mixtures of *ortho,para*-isomers result from a reaction, usually separation into components by fractional distillation is either very difficult or impossible because the boiling point separation is very small. There are a number of exceptions to this generalization, for example, the *o*- and *p*-nitrotoluenes (p. 461), nitrophenols (p. 507), and hydroxybenzaldehydes (p 522), where chelation through hydrogen bonding is believed to take place in the *ortho*-isomer. The usual boiling point separation of isomeric *ortho*- and *para*-halogen compounds is two or three degrees, although sometimes it is greater, as with the dichlorobenzenes (Table 83). The presence of any *meta*-isomer in the reaction mixture usually decreases the effectiveness of distillation. Separation by crystallization allows one product to be obtained pure, but usually not quantitatively.

TABLE 83 | Some Aromatic Halogen Compounds

	m.p. °C	b.p °C	*ortho*		*meta*		*para*	
			m p °C	b.p. °C	m p. °C	b p. °C	m p. °C	b p. °C
Fluorobenzene		85.05						
Chlorobenzene	−45 2	132.0						
Bromobenzene	−30.6	156 2						
Iodobenzene	−31.4	188 6						
Fluorotoluene				115	−110 8	115		116
Chlorotoluene			−34 0	159 2	−47.8	162	7.8	162.4
Bromotoluene			−25.75	181.7	−39.8	183.7	28	185
Iodotoluene				206.1		210 6	35	211
Benzyl chloride	−41.2	179.3						
Benzal chloride	−16.4	205.1						
Benzotrichloride	−4.8	220.7						
Benzyl bromide	−3.9	201						
Difluorobenzene			−34	92	−59	83	−13	88.6
Dichlorobenzene			−16 7	180 3	−24 4	173.0	52.1	174.5
Dibromobenzene			6.7	221	−6 9	217 0	87.2	219
Diiodobenzene			26 7	286 8	35 4	284 8	129 2	285
Chlorobromobenzene			−12 1	204	−21.2	197	67.4	196
Chloroiodobenzene			0.7	235		230	56	227
Bromoiodobenzene			2 1(5 0)	257 4	−9.3	252	90 5	251

When bromobenzene is brominated in the presence of ferric bromide, the mixture of dibromobenzenes has: *ortho*, 13 per cent; *meta*, 2 per cent; and *para*, 85 per cent. When this mixture is cooled, some of the *para*-isomer will crystallize out. The amount that could be obtained on cooling, in the absence of any *meta*-isomer, is shown by Figure 29, where the melting point of *ortho,para*-mixtures is plotted against the composition. The melting point of the reaction mixture is about 75°, shown by point *A*. As the temperature is lowered, *para*-dibromobenzene slowly crystallizes out and at 20°, after equilibrium has been established, the composition of the liquid in equilibrium

with the solid is about 23 per cent *para*, point *B*. Further cooling to 0.3°, the eutectic point, causes a further separation of the *para*-isomer, the liquid having about 12 per cent *para*. The solid would be pure if there were some way by which it could be separated completely from the liquid. However, since the surface of the solid is wet with the eutectic mixture, crystallization from a suitable solvent is necessary for complete purification. The theoretical amount that can be recovered by crystallization (assuming 86% *para* and 14% *ortho* initially) is 95 per cent of the *para* originally present.

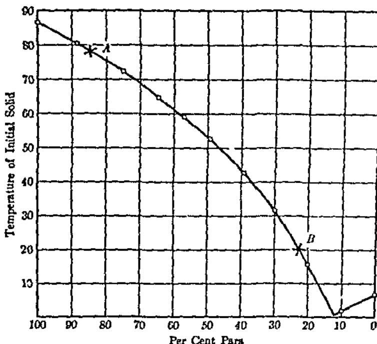


Figure 29 • Melting-Point Curve of Ortho and Para Dibromobenzenes

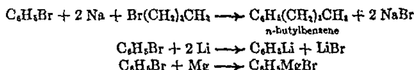
Obtaining the pure *ortho*-isomer from the reaction mixture is not easy. On further cooling of the eutectic mixture below 0° the *ortho*- and *para*-isomers both crystallize. By careful supercooling, then seeding with pure *ortho*, it may be possible to obtain a crop of *ortho*, or by seeding with pure *para*, to obtain still more *para*. The latter would bring the composition of the liquid below 12 per cent *para*, *i.e.*, above 88 per cent *ortho*. Then on cooling this to 0°, some pure *ortho* can be made to crystallize. *The small separation of boiling points (para, 219°; ortho, 221°) means a rather laborious fractional* distillation, but with a modern efficient fractionation apparatus it would be feasible, more particularly if applied to the eutectic mixture.

When the isomers to be separated have such high melting points that the melting point of the eutectic mixture is well above room temperature, advantage can be taken of the principle that of two similar solids the lower melting one is more soluble in solvents. The mixture can be shaken quickly with a suitable solvent so as to dissolve much *ortho* and only a small amount of *para*. Crystallization from the resulting solution often yields the desired isomer.

Sometimes a chemical method is available. For separating *ortho*- and *para*-dibromobenzenes, heating the mixture with concentrated sulfuric acid causes sulfonation of the *ortho*-form. This is removed partly by solution in the sulfuric acid and completely by shaking with water, while the para-isomer remains insoluble. The *ortho*-isomer is regenerated from the sulfonic acid (Chap. 30).

Reactions of Halogen Compounds. There is a marked difference in the reactivity of aryl and aralkyl halides. The benzene ring deactivates aryl halides, C_6H_5X, and activates those of the benzyl type, $C_6H_5CH_2X$, where the halogen atom is attached to a carbon atom attached to the ring.

1. *Aryl halides.* These resemble vinyl halides (p. 116) in being unreactive at room temperature or even at 100° with most of the chemicals that react with alkyl halides, for example, strong bases, salts of weak acids (including sodiomalonic and sodioacetoacetic esters), silver nitrate (aqueous or alcoholic), ammonia, and amines. The halogen atom is not eliminated as hydrogen halide in the presence of aluminum halide. Aryl bromides react with some metals; with sodium they undergo the Wurtz-Fittig reaction, with lithium they form organolithium compounds, and with magnesium, Grignard reagents. Some aryl chlorides react likewise; for example, chlorobenzene forms a Grignard reagent.



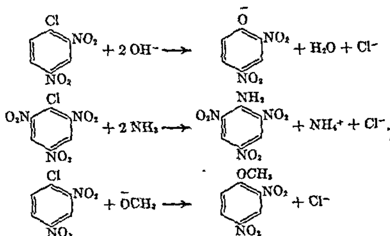
$$C_6H_5Br + 2\,Na + Br(CH_2)_3CH_3 \longrightarrow \underset{n\text{-butylbenzene}}{C_6H_5(CH_2)_3CH_3} + 2\,NaBr$$

$$C_6H_5Br + 2\,Li \longrightarrow C_6H_5Li + LiBr$$

$$C_6H_5Br + Mg \longrightarrow C_6H_5MgBr$$

Chlorobenzene reacts with sodium hydroxide at 300 to 350° in the presence of metallic copper, and with ammonia at 200° in the presence of cuprous oxide (p. 452).

Aryl halogen compounds are made more reactive towards electrophilic reagents by the presence of nitro groups in *ortho-* and *para-*positions; 2,4-dinitrochlorobenzene and 2,4,6-trinitrochlorobenzene when heated with aqueous alcoholic potassium hydroxide are converted into phenols. Reaction takes place also with ammonia and metallic alkoxides.

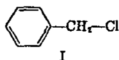


2. *Aralkyl halides.* Benzyl halides resemble allyl halides in their reactivity (p. 117). Those halides with halogen further out on the side chain resemble alkyl halides in reactivity (p. 109).

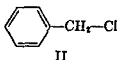
Reactivity as Affected by Resonance. The belief that chlorobenzene is a resonance hybrid of the forms XVIII to XXII shown on page 442 is based on the observation that the carbon-to-chlorine distance is 1.69 Å, whereas in methyl chloride and chloroform it is 1.77 Å. This bond shortening indicates a considerable amount (15%) of double-bond character, resulting from the contribution of the three resonating forms having this double bond. This modification of the bond character decreases the reactivity of the molecule because the chlorine atom cannot easily separate as chloride ion. Chlorobenzene is like vinyl chloride in reactivity in displacement reactions, and in having a short carbon-to-chlorine bond (p. 116).

The effect of nitro groups in enhancing reactivity towards nucleophilic reagents can be accounted for in terms of resonance. It will be recalled that nucleophilic reagents react with carbon atoms that are at the positive ends of dipoles (alkyl halides, p. 108), or are positively charged because of resonance (carbonyl compounds, p. 128). The resonance forms of chlorobenzene, 2-nitrochlorobenzene, and 2,4-dinitrochlorobenzene should next be considered. Among the five resonance forms of chlorobenzene, there are none in which the carbon atom holding the chlorine atom is positively charged. Among the eight resonance forms of 2-chloronitrobenzene, one has such a positively charged atom, and among the twenty-four resonance forms of 2,4-dinitrochlorobenzene, four have such an atom. Thus the percentage contribution of reactive forms is greater, the larger the number of nitro groups present in *o*- and/or *p*-positions to the halogen atom. A nucleophilic reagent, for example hydroxide ion, can on this account react better with 2,4-dinitrochlorobenzene, by coordinating with the positively charged carbon atom and expelling the chlorine atom as chloride ion. It will be recalled that the iodine atom of ethyl iodide is expelled as iodide ion in the reaction with hydroxide ion (p. 109).

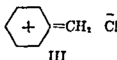
The enhanced reactivity of benzyl halides also can be ascribed to resonance; in such cases the resonance resembles that occurring in propargyl chloride (p. 116); it involves forms I, II, and III, where I and II are the two Kekulé forms and III represents three other electronic forms (see p. 442).



I



II

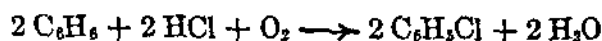


III

These last three illustrate hyperconjugation, or no-bond resonance (p. 443), and place a formal negative charge on the chlorine atom. This can more easily leave the molecule in the form of chloride ion, in comparison to an alkyl halide.

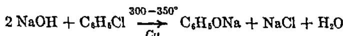
Chlorobenzene, C_6H_5Cl. This is easily prepared by passing chlorine into benzene containing a small amount of anhydrous ferric chloride, usually formed by the reaction of chlorine with a small amount of added metallic iron (filings, tacks, etc.). Some dichlorobenzene (*ortho,para*-mixture) is formed at the same time. Other catalysts,

may be used (p. 446). An industrial development for chlorobenzene is a combination of *oxidation*, as in the Deacon process of chlorine manufacture, and *substitution*, so that benzene is converted into chlorobenzene by passing benzene, hydrogen chloride, and oxygen (or air) through a hot reaction zone over a suitable copper catalyst.



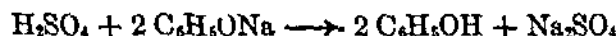
$$2\,C_6H_6 + 2\,HCl + O_2 \longrightarrow 2\,C_6H_5Cl + 2\,H_2O$$

Although the chlorine of chlorobenzene is chemically inert, reaction takes place at elevated temperatures; also, reactions involving the ring take place. An industrial method for the production of phenol, C_6H_5OH, is based on the reaction with sodium hydroxide at 300 to 350° in the presence of metallic copper, a metal that often increases the reactivity of aromatic compounds.



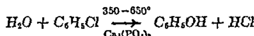
$$2\,NaOH + C_6H_5Cl \xrightarrow[Cu]{300-350^\circ} C_6H_5ONa + NaCl + H_2O$$

Pressure equipment is necessary. Phenol is obtained by the addition of a suitable acid



$$H_2SO_4 + 2\,C_6H_5ONa \longrightarrow 2\,C_6H_5OH + Na_2SO_4$$

Another industrial method for phenol is hydrolysis with steam at elevated temperatures over a suitable catalyst, for example, tricalcium phosphate.



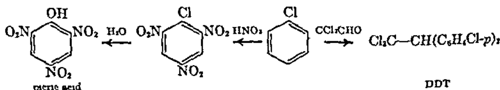
$$H_2O + C_6H_5Cl \xrightarrow[Ca_3(PO_4)_2]{350-650^\circ} C_6H_5OH + HCl$$

An industrial method for aniline, $C_6H_5NH_2$, is ammonolysis at 200° and in the presence of cuprous oxide.



$$2\,NH_3 + Cu_2O + 2\,C_6H_5Cl \longrightarrow 2\,C_6H_5NH_2 + Cu_2Cl_2 + H_2O$$

Important reactions on the ring are nitration, condensation with chloral (p. 555), and condensation with phthalic anhydride (see p. 531). Nitration gives 2,4,6-tri*nitrochlorobenzene and this on hydrolysis is converted to picric acid.* This is an important industrial method. Condensation with choral gives the insecticide, DDT (p. 555).



Bromobenzene, C_6H_5Br, is easily prepared from benzene, bromine, and iron filings. It is reactive with metals. It enters into the Wurtz-Fittig reaction with metallic sodium (p. 428) and readily yields a Grignard reagent, C_6H_5MgBr, useful for forming a carbon bond to the benzene ring.

Iodobenzene, C_6H_5I. The most convenient method of preparation is from benzenediazonium sulfate and potassium iodide (p. 486). Its greatest interest lies in a number of related compounds in which the iodine atom is combined also with chlorine [illegible] of higher acid,

Phenyliodoso Chloride. This results when chlorine is passed into a solution of iodobenzene in a solvent (chloroform).



$$Cl_2 + C_6H_5I \longrightarrow C_6H_5ICl_2$$

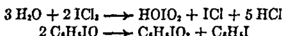
Iodosobenzene, C_6H_5IO. This results from the action of a base on phenyliodoso chloride.



$$2\,KOH + C_6H_5ICl_2 \longrightarrow C_6H_5\!-\!\overset{+}{I}\!-\!\overset{-}{O} + 2\,KCl + H_2O$$

The structure probably involves other resonance forms, one with a double bond between iodine and oxygen, others with the positive charge on the ring.

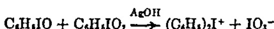
Iodoxybenzene, $C_6H_5IO_2$. This is formed, along with iodobenzene, when iodosobenzene is heated. The reaction is one of disproportionation, or in this case, simultaneous oxidation and reduction, similar to the one undergone by iodine trichloride when it is heated in water.



$$3\,H_2O + 2\,ICl_3 \longrightarrow HOIO_2 + ICl + 5\,HCl$$
$$2\,C_6H_5IO \longrightarrow C_6H_5IO_2 + C_6H_5I$$

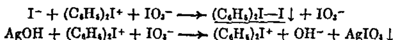
Iodoxybenzene is unstable and explodes when heated to about 230°.

Diphenyliodonium Compounds. An unusual reaction takes place between iodosobenzene and iodoxybenzene in the presence of a base, which acts catalytically.



$$C_6H_5IO + C_6H_5IO_2 \xrightarrow{AgOH} (C_6H_5)_2I^+ + IO_3^-$$

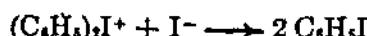
The product is diphenyliodonium iodate, soluble in water. On the addition of a reducing agent (sodium bisulfite) or of iodide ion to an aqueous solution of the iodate, the sparingly soluble diphenyliodonium iodide is precipitated; on the addition of an excess of silver hydroxide, silver iodate is precipitated, and diphenyliodonium hydroxide is formed.



$$I^- + (C_6H_5)_2I^+ + IO_3^- \longrightarrow \underline{(C_6H_5)_2I\!-\!I}\downarrow + IO_3^-$$
$$AgOH + (C_6H_5)_2I^+ + IO_3^- \longrightarrow (C_6H_5)_2I^+ + OH^- + \underline{AgIO_3}\downarrow$$

Diphenyliodonium hydroxide is completely ionized in aqueous solution and causes the same rate of hydrolysis of methyl acetate as does sodium hydroxide. It is, therefore, as strong a base as sodium hydroxide. In this respect it resembles trimethylsulfonium hydroxide and tetramethylammonium hydroxide. It reacts with acids to yield the corresponding salt, for example, with hydriodic acid it forms diphenyliodonium iodide.

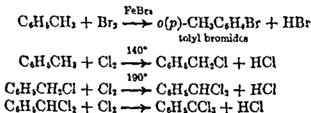
Th[illegible]
than [illegible]
the se[illegible]
namely 3.54 Å. The iodonium iodine has a complete octet. In order for a covalent bond to be formed between the two iodine atoms, one of them would have to expand its octet. The iodide when heated decomposes to iodobenzene.



$$(C_6H_5)_2I^+ + I^- \longrightarrow 2\,C_6H_5I$$

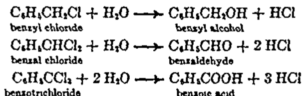
Other Aryl and Alkaryl Halides. The most important are those derived from toluene, which undergoes ring substitution very readily with a small amount of suitable

catalyst, and side-chain substitution above 100°, especially when illuminated. Side-chain substitution is the more important reaction.



$$C_6H_5CH_3 + Br_2 \xrightarrow{FeBr_3} o(p)\text{-}CH_3C_6H_4Br + HBr \quad \text{(tolyl bromides)}$$
$$C_6H_5CH_3 + Cl_2 \xrightarrow{140°} C_6H_5CH_2Cl + HCl$$
$$C_6H_5CH_2Cl + Cl_2 \xrightarrow{190°} C_6H_5CHCl_2 + HCl$$
$$C_6H_5CHCl_2 + Cl_2 \longrightarrow C_6H_5CCl_3 + HCl$$

If the reaction is carried out with liquid toluene, a mixture results because some of the benzyl chloride undergoes substitution. By carrying out the reaction in the vapor phase at a temperature between the boiling points of toluene and benzyl chloride, the latter is obtained in excellent yield because it condenses out and thus escapes further reaction. The names of the compounds are related to the products obtained when they are boiled with water.



$$\underset{\text{benzyl chloride}}{C_6H_5CH_2Cl} + H_2O \longrightarrow \underset{\text{benzyl alcohol}}{C_6H_5CH_2OH} + HCl$$
$$\underset{\text{benzal chloride}}{C_6H_5CHCl_2} + H_2O \longrightarrow \underset{\text{benzaldehyde}}{C_6H_5CHO} + 2\,HCl$$
$$\underset{\text{benzotrichloride}}{C_6H_5CCl_3} + 2\,H_2O \longrightarrow \underset{\text{benzoic acid}}{C_6H_5COOH} + 3\,HCl$$

These are important industrial reactions. Usually a base is added to the water to give a faster rate, except when benzaldehyde is being formed, because a strong base causes it to undergo dismutation. Chalk is added to neutralize the acid. *Oxidation* converts benzyl and benzal chlorides to benzoic acid. Benzyl chloride is a very reactive compound (p. 450).

Benzyl halides are eye irritants and cause tears to flow. Benzyl chloride is a lachrymator. More effective are xylyl bromide, $CH_3C_6H_4CH_2Br$, and chloroacetophenone (phenacyl chloride), $C_6H_5COCH_2Cl$, which was used extensively in World War I as a lachrymator. Still more powerful is bromobenzyl cyanide, $C_6H_5CHBrCN$, which at a concentration of 3×10^{-7} g. per liter causes a flow of tears. It also was used in World War I.

PROBLEMS

1. Using only halogenation methods, show how the following may be prepared from hydrocarbons found in coal tar, stating reagents and conditions, and assuming that a solid *para*-isomer can be obtained pure from an *ortho,para*-mixture.

a) *p*-chlorobromobenzene
b) *p*-chloroiodobenzene
c) *p*-chlorobenzyl chloride
d) *p*-chlorobenzyl bromide
e) *p*-chloroiodosobenzene
f) *p*-bromoiodosobenzene
g) *m*-methylbenzyl chloride
h) 4-chloro-*m*-xylene
i) *p*-methylbenzyl bromide
j) *p*-bromobenzyl bromide
k) *o*-methylbenzyl chloride
l) 4-bromo-*m*-xylene
m) *p*-bromobenzyl chloride
n) *p*-methylbenzyl chloride

2. Describe a chemical test, stating reagent, conditions, solvent if any, and readily detectable change, that serves to distinguish between:

a) chlorobenzene and 1-chlorohexane
b) phenyl chloride and *n*-butyl chloride
c) benzyl bromide and *p*-bromotoluene
d) *m*-dibromobenzene and *m*-bromobenzyl bromide
e) benzyl chloride and *o*-chlorotoluene
f) bromobenzene and 2-bromohexane
g) benzyl bromide and 1-bromohexane
h) α-chloro-*p*-xylene and *p*-chlorotoluene
i) *p*-chlorobenzyl chloride and α,β-dichloroethylbenzene
j) α-chloro-*m*-xylene and 4-chloro-*m*-xylene
k) benzyl bromide and α-bromoethylbenzene
l) benzyl bromide and α,β-dibromoethylbenzene

3. *Show how the following may be obtained from bromobenzene, stating reagents and* conditions, and assuming that a solid *para*-isomer can be obtained pure from an *ortho,para*-mixture.

a) 2-chloro-1,4-dibromobenzene
b) benzene
c) *n*-propylbenzene
d) *p*-bromonitrobenzene
e) benzoic acid
f) methylphenylcarbinol
g) methylethylcarbinol
h) styrene
i) styrene bromide
j) isopropylbenzene
k) α-bromoethylbenzene
l) *p*-bromobenzenesulfonic acid
m) dimethylphenylcarbinol
n) α-chloro-*m*-xylene
o) *p*-xylene
p) α-chloro-*p*-xylene

4. Compound *A*, insoluble in water, caused a slow reduction when heated under a reflux condenser with aqueous alkaline potassium permanganate. Addition of excess hydrochloric acid to the solution remaining after the precipitate was removed caused a solid, *B*, to separate. The formulas of *A* and *B* are given below and with these are the number of theoretically possible structurally isomeric mononitro substitution products of *B*. Write a possible structural formula for both *A* and *B*.

a) C_8H_9Br, $C_7H_5O_2Br$, two
b) C_8H_9Br, $C_8H_6O_4$, two
c) $C_9H_{11}Br$, $C_9H_6O_6$, one
d) $C_9H_{11}Br$, $C_8H_6O_4$, two
e) $C_9H_{11}Br$, $C_8H_6O_4$, three
f) $C_{10}H_{13}Br$, $C_8H_6O_4$, one

5. Compound *A* has the number of monobromo structurally isomeric substitution products indicated by the number following the formula. It reacts as described for *A* in problem 4. The number of theoretically possible structurally isomeric monobromo substitution products of *B* are indicated by the number following the formula. Write a possible structural formula for both *A* and *B*.

a) C_8H_9Cl, five, $C_8H_5O_4Cl$, three
b) $C_9H_{11}Cl$, six, $C_7H_6O_2$, three
c) $C_9H_{11}Cl$, five, $C_8H_6O_4$, one
d) $C_9H_{11}Cl$, seven, $C_7H_5O_2Cl$, four
e) $C_{10}H_{13}Cl$, seven, $C_8H_5O_4Cl$, three
f) $C_{10}H_{12}Cl_2$, three, $C_7H_4O_2Cl_2$, two
g) $C_{10}H_{13}Cl$, five, $C_8H_6O_4$, one
h) $C_{10}H_{12}Cl_2$, four, $C_8H_6O_4$, two

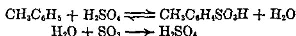
CHAPTER 30

Sulfonic Acids; Nitro Compounds; Azo Compounds

The most characteristic and from an industrial point of view the most important reactions of the aromatic hydrocarbons are sulfonation and nitration. It is possible to differentiate between aromatic and saturated aliphatic hydrocarbons by means of these reactions. The operations of sulfonation and nitration are carried out on a large scale in the manufacture of dyes, explosives, and other products.

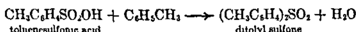
SULFONIC ACIDS

Preparation. The sulfonation reaction can be carried out with concentrated sulfuric acid but usually fuming sulfuric acid, containing dissolved sulfur trioxide, is better. Benzene reacts only slowly with concentrated acid, toluene somewhat more rapidly, but in either case the reaction is incomplete. The reaction can be made fairly complete by removal of the water formed, as by azeotropic distillation with the hydrocarbon or by the use of fuming acid.



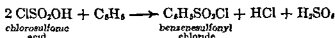
$$CH_3C_6H_5 + H_2SO_4 \rightleftharpoons CH_3C_6H_4SO_3H + H_2O$$
$$H_2O + SO_3 \longrightarrow H_2SO_4$$

A side reaction is sulfone formation which is due to a reaction of the sulfonic acid with hydrocarbon.



$$\underset{\text{toluenesulfonic acid}}{CH_3C_6H_4SO_2OH} + C_6H_5CH_3 \longrightarrow \underset{\text{ditolyl sulfone}}{(CH_3C_6H_4)_2SO_2} + H_2O$$

An especially effective sulfonating agent is chlorosulfonic acid, which produces the acid chloride of the sulfonic acid.



$$2\ \underset{\text{chlorosulfonic acid}}{ClSO_2OH} + C_6H_6 \longrightarrow \underset{\text{benzenesulfonyl chloride}}{C_6H_5SO_2Cl} + HCl + H_2SO_4$$

Dilution of the reaction mixture with water does not take place because, like sulfur trioxide, chlorosulfonic acid reacts rapidly with water.



$$H_2O + ClSO_2OH \longrightarrow HCl + H_2SO_4$$

The sulfonation of aromatic compounds in general follows the rules governing substitution (Chap. 28). High temperature in general favors the *para* and low temperature leads to an increase in the amount of *ortho*. This is

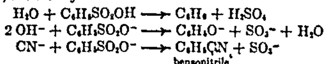
truè of toluene, which is sulfonated with chlorosulfonic acid when the *ortho*-isomer is desired.

The sulfonic acid must be separated from a considerable amount of unreacted sulfuric acid. Sulfonic acids usually are very soluble in water. Separation is brought about differently: (1) sometimes the solubility of the sulfonic acid is low enough in cold, concentrated hydrochloric acid to effect separation; (2) many sodium or potassium salts are much less soluble in water than the corresponding bisulfates, and thus the acids are separated from each other in salt form; (3) most calcium and barium arylsulfonates are soluble in water, whereas the sulfates are not; (4) the sulfonchlorides are insoluble in water, soluble in benzene and other typical organic solvents, just the reverse of sulfuric acid. The free sulfonic acids can be obtained from the calcium or barium salts by metathesis with the correct amount of sulfuric acid, or from the sulfonchlorides by boiling with water, but not so easily from sodium or potassium salts. However, these can be converted into the corresponding sulfonchlorides.

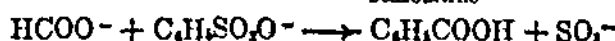
Properties of Sulfonic Acids. The acids are solids, very soluble in water, insoluble in hydrocarbons and halogenated hydrocarbons, and nondistillable at atmospheric pressure because of decomposition. At very low pressures some can be distilled. Sulfonic acids are strong acids, much stronger than the carboxylic acids and comparable in strength to sulfuric acid. The sulfonic acid group (sulfo group) often is introduced into large molecules, particularly those of azo dyes, for the purpose of increasing the solubility in water, sometimes as the free acid but usually as a salt.

Reactions. These are of two types, *viz.*, (1) replacement and (2) conversion of the sulfonic acid group to a related functional group.

1. *Replacement reactions.* The sulfonic acid group may be replaced by hydrogen, hydroxyl, cyano, or carboxyl. When heated with water at 150 to 160°, the sulfonation reaction is reversed. When the sodium (or potassium) salt is heated with sodium (or potassium) hydroxide, the salt of a phenol is formed; when heated with sodium cyanide, a nitrile is formed; and when with sodium formate, a carboxylic acid.

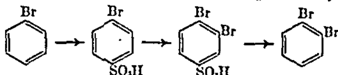


$$H_2O + C_6H_5SO_2OH \longrightarrow C_6H_6 + H_2SO_4$$
$$2\,OH^- + C_6H_5SO_2O^- \longrightarrow C_6H_5O^- + SO_3^{=} + H_2O$$
$$CN^- + C_6H_5SO_2O^- \longrightarrow \underset{\text{benzonitrile}}{C_6H_5CN} + SO_3^{=}$$

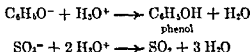


$$HCOO^- + C_6H_5SO_2O^- \longrightarrow C_6H_5COOH + SO_3^{=}$$

The reverse of the sulfonation reaction is employed after a sulfo group has served some special purpose, for example, blocking off some particular position or directing an entering substituent to some other position. The formation of *o*-dibromobenzene from bromobenzene is a good example.



An important method for the manufacture of phenol has been based on the reaction with sodium hydroxide. Phenol results when an acid is added to the reaction mixture, and sulfur dioxide is evolved.

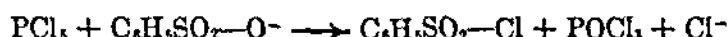


$$C_6H_5O^- + H_3O^+ \longrightarrow \underset{\text{phenol}}{C_6H_5OH} + H_2O$$

$$SO_3^{=} + 2\,H_3O^+ \longrightarrow SO_2 + 3\,H_2O$$

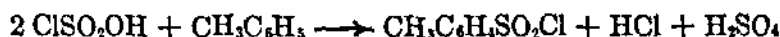
From the standpoint of convenience, the hydroxy, cyano, and carboxy groups usually are introduced *via* the diazo reaction (Chap. 32) rather than from a sulfonic acid.

2. *Conversion to related compounds; sulfonyl chlorides.* Like carboxylic acids, sulfonic acids can be converted to acid halides, and these to amides or esters. Phosphorus pentachloride is a good reagent for converting benzenesulfonic acid (preferably as a salt) to benzenesulfonyl chloride (benzenesulfonchloride) and for the preparation of other sulfonyl chlorides.



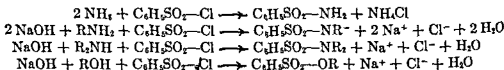
$$PCl_5 + C_6H_5SO_2{-}O^- \longrightarrow C_6H_5SO_2{-}Cl + POCl_3 + Cl^-$$

Sulfonyl chlorides can be obtained also from hydrocarbons by chlorosulfonation with chlorosulfonic acid (p. 456), which is especially useful for the preparation of the toluenesulfonic acids. The *ortho*-isomer is important in the preparation of saccharin (p. 534), and the *para*, of chloramine T. At 0 to 5° about a 60 per cent yield of *o*-toluenesulfonyl chloride can be obtained by a combination of crystallization (to remove most of the *para*-isomer) and distillation under reduced pressure (Table 84)



$$2\,ClSO_2OH + CH_3C_6H_5 \longrightarrow CH_3C_6H_4SO_2Cl + HCl + H_2SO_4$$

Sulfonchlorides resemble acyl chlorides in the reactions they undergo, except that sometimes they are more sluggish.



$$2\,NH_3 + C_6H_5SO_2{-}Cl \longrightarrow C_6H_5SO_2{-}NH_2 + NH_4Cl$$

$$2\,NaOH + RNH_2 + C_6H_5SO_2{-}Cl \longrightarrow C_6H_5SO_2{-}NR^- + 2\,Na^+ + Cl^- + 2\,H_2O$$

$$NaOH + R_2NH + C_6H_5SO_2{-}Cl \longrightarrow C_6H_5SO_2{-}NR_2 + Na^+ + Cl^- + H_2O$$

$$NaOH + ROH + C_6H_5SO_2{-}Cl \longrightarrow C_6H_5SO_2{-}OR + Na^+ + Cl^- + H_2O$$

When a sulfonchloride reacts with ammonia, or with a primary or secondary amine, only half of the base reacts because part is converted into a salt of hydrochloric acid. In order to obtain complete conversion, a second base should be present, either an inorganic base or a tertiary amine (see p. 220). Likewise, when an alcohol, for example, ethyl alcohol, is being converted to an ester, for example, ethyl benzenesulfonate, an inorganic base or, preferably, a tertiary amine should be present.

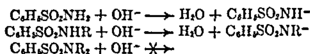
Sulfonamides; Hinsberg Test for Primary, Secondary, and Tertiary Amines. In many respects these resemble amides of carboxylic acids, and differ in some respects, *viz.*, sulfonamides usually have higher melting points and lower solubilities in water than the corresponding amides, and are much stronger acids (Table 84). These properties make them valuable in the detection and identification of amines, and form the basis of the Hinsberg method of distinguishing primary, secondary, and tertiary

TABLE 84 | Constants of Some Sulfonic Acids and Derivatives

ACID	FORMULA	M.P. °C	BOILING POINT temp °C	BOILING POINT press. mm.	SOLY. IN H_2O G./100 G. 25°	K_a
Benzenesulfonic	$C_6H_5SO_3H \cdot 1\frac{1}{2}\ H_2O$	66 [a]	171–172	0 1	v. sol.	large
o-Toluenesulfonic	$CH_3C_6H_4SO_3H \cdot 2\ H_2O$	[b]			v. sol.	large
m-Toluenesulfonic	$CH_3C_6H_4SO_3H$	[c]				
p-Toluenesulfonic	$CH_3C_6H_4SO_3H \cdot H_2O$	38 [d]	185–187	0 1	v. sol.	large
DERIVATIVE						
Benzenesulfonamide	$C_6H_5SO_2NH_2$	153			0 43 [e]	1×10^{-10}
[illegible]	[illegible]	156.3			0.16	
[illegible]	[illegible]	108			0.78	
[illegible]	[illegible]	137.5			0 3	9×10^{-11}
Benzenesulfonyl chloride	$C_6H_5SO_2Cl$	14.6	251.5 118–120	760 15	insol.	
o-Toluenesulfonyl chloride	$CH_3C_6H_4SO_2Cl$	10	126	10	insol.	
m-Toluenesulfonyl chloride	$CH_3C_6H_4SO_2Cl$	11.7			insol.	
p-Toluenesulfonyl chloride	$CH_3C_6H_4SO_2Cl$	69	145–146	150	insol.	
Diphenyl sulfone	$C_6H_5SO_2C_6H_5$	128	379 230	760 15	insol.	
Di-p-tolyl sulfone	$(CH_3C_6H_4)_2SO_2$	159	405	713	insol.	

[a] Anhydrous; hydrated, 44°. [b] m p. < 100°, at 140–150°, slowly changes to *p*-isomer. [c] Sirup. [d] Anhydrous; hydrated, 106°. [e] At 16°.

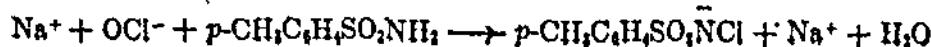
amines. *Amides having one or two hydrogen atoms attached to nitrogen are acidic* and with strong bases form salts soluble in water. Those having no hydrogen are neutral (Table 84). An aryl sulfonyl group is a strongly electronegative group (Table 16, p. 35), enhancing acidic properties and diminishing basic properties.



$$C_6H_5SO_2NH_2 + OH^- \longrightarrow H_2O + C_6H_5SO_2NH^-$$
$$C_6H_5SO_2NHR + OH^- \longrightarrow H_2O + C_6H_5SO_2NR^-$$
$$C_6H_5SO_2NR_2 + OH^- \not\rightleftharpoons$$

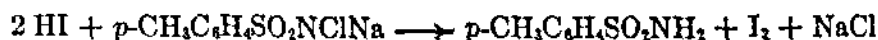
As reaction takes place between an amine and benzenesulfonyl chloride in the presence of aqueous sodium hydroxide, a primary amine forms a water-soluble sulfonamide, and a secondary forms an insoluble derivative. A tertiary amine does not react. If this was insoluble to start with, it still remains insoluble. Then on the addition of hydrochloric acid to the reaction mixture, the derivative of the primary amine is precipitated, that of the secondary is not affected, and any insoluble tertiary amine dissolves.

Chloramine-T, Sodium N-Chloro-*p*-toluenesulfonamide, Chlorazine. This is formed by the action of sodium hypochlorite on *p*-toluenesulfonamide.



$$Na^+ + OCl^- + p\text{-}CH_3C_6H_4SO_2NH_2 \longrightarrow p\text{-}CH_3C_6H_4SO_2\bar{N}Cl + Na^+ + H_2O$$

It is a stable, water soluble compound that liberates iodine from iodide ion under acidic conditions.



$$2\,HI + p\text{-}CH_3C_6H_4SO_2NClNa \longrightarrow p\text{-}CH_3C_6H_4SO_2NH_2 + I_2 + NaCl$$

Chloramine-T is a valuable antiseptic. It is used also as a standard in iodometric titrations The free sulfonamide is unstable, whereas the salt is stable.

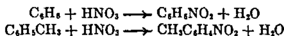
Identification of Sulfonic Acids. An aromatic sulfonic acid may be detected by fusing it for a short time with solid potassium hydroxide, then adding an excess of *strong acid to the aqueous solution of the product. An odor of sulfur dioxide* and the formation of a brominated phenol when bromine water is added to the resulting acidic solution indicate that the original compound probably was an aromatic sulfonic acid. Identification may be made complete by converting the acid (or the salt) to the amide, *via* the sulfonyl chloride. The amides are solids with known melting points.

NITRO COMPOUNDS

Derivatives of aromatic hydrocarbons having a nitro group attached to a side chain resemble aliphatic nitro compounds in their general behavior. Those in which it is attached to the benzene ring are the important group, and are the true aryl nitro compounds. Nitro compounds are intermediates in the manufacture of amines; they sometimes serve as mild oxidation agents, as in fuchsine preparation. Tri- and polynitro compounds are employed as explosives (TNT, for example).

The usual method of preparation is direct nitration, and a mixture of concentrated nitric and sulfuric acids is the usual nitration mixture. More powerful mixtures are anhydrous (fuming) nitric acid and concentrated sulfuric acid, sodium or potassium nitrate with concentrated sulfuric acid, and still more powerful, anhydrous nitric acid and fuming sulfuric acid (containing dissolved sulfur trioxide). For nitrating reactive compounds (hydroxy compounds, acyl derivatives of amines, ethers) nitric acid (concentrated or fuming) in glacial acetic acid often is used. The presence of sulfuric acid usually increases the rate of nitration, decreases the rate of the undesirable side reactions of oxidation, and permits the nitration to be carried out at a higher temperature. A probable mechanism of nitration is proposed in Chapter 28, page 440.

Benzene undergoes easy nitration to nitrobenzene, and toluene to a mixture, mainly *o*- and *p*-nitrotoluenes, with the usual nitration mixture.



$$C_6H_6 + HNO_3 \longrightarrow C_6H_5NO_2 + H_2O$$
$$C_6H_5CH_3 + HNO_3 \longrightarrow CH_3C_6H_4NO_2 + H_2O$$

The presence of one nitro group in the molecule decreases the ease of introducing a second such group, and the presence of two necessitates the use of powerful nitrating mixtures. Yields of trinitrobenzene are extremely poor, because of oxidation, but trinitrotoluene can be obtained in good yield, owing to the activating influence of the methyl group.

Nitro compounds are insoluble in and heavier than water, soluble in the common organic solvents and in concentrated sulfuric acid. They usually

have a pale yellow color and a characteristic aromatic odor. This is so intense in some compounds that they are used in perfumery. For example, 2,4,6-trinitro-3-*tert*-butyltoluene and 2,4,6-trinitro-5-*tert*-butyl-*m*-xylene are known as nitro musks.

TABLE 85 | Some Nitro Compounds

NAME	FORMULA	M.P. °C	B.P. °C
Nitrobenzene	$C_6H_5NO_2$	5.67	210.9
o-Nitrotoluene	1,2-$CH_3C_6H_4NO_2$	α, −9.5 β, −3.4	222.3
m-Nitrotoluene	1,3-$CH_3C_6H_4NO_2$	15.5	231.8
p-Nitrotoluene	1,4-$CH_3C_6H_4NO_2$	51.6	238.3
α-Nitrotoluene	$C_6H_5CH_2NO_2$		225–227 [a] 118–119 [b]
m-Dinitrobenzene	1,3-$C_6H_4(NO_2)_2$	90.0	297
1,3,5-Trinitrobenzene	$C_6H_3(NO_2)_3$	122.5	167 [c]
2,4-Dinitrotoluene	$CH_3C_6H_3(NO_2)_2$	70.1	300 [a]
2,4,6-Trinitrotoluene	$CH_3C_6H_2(NO_2)_3$	80.5	expl 240
o-Nitroacetanilide	1,2-$NO_2C_6H_4NHAc$	93	
m-Nitroacetanilide	1,3-$NO_2C_6H_4NHAc$	155	
p-Nitroacetanilide	1,4-$NO_2C_6H_4NHAc$	214	
Nitrosobenzene	C_6H_5NO	68	
N-Phenylhydroxylamine	C_6H_5NHOH	82	

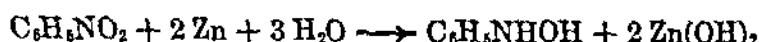
[a] With decomposition. [b] At 16 mm. [c] At 14 mm

Reactions. The effect of the nitro group on ring substitution is a decreased rate and *meta*-orientation (Chap. 28). Also it inhibits the Friedel-Crafts reaction unless a strongly activating group, such as hydroxyl, is also present.

The principal reaction of the nitro group is reduction, and the principal *reduction reaction is the one yielding a primary amine. The oxidizing action* of a nitro group is shown not only by reaction with numerous reducing agents, but also by instability of certain nitro compounds, in particular the di- and polynitro compounds. Some dinitro compounds, for example dinitrobenzene, decompose when attempt is made to distil them, and many trinitro and polynitro compounds decompose explosively under shock or when heated in a closed vessel. Nitrobenzene is taken as a typical compound.

1. *Effect of alkalies.* When one nitro group is present and is attached to a ring-carbon atom, the compound resembles a tertiary aliphatic nitro compound in not dissolving in aqueous strong base, whereas a secondary or primary nitroparaffin does. Under alkaline conditions intramolecular oxidation and reduction sometimes take place. For example, when *o*-nitrotoluene is heated with concentrated aqueous sodium hydroxide there is formed a black, tarry mass from which *o*-aminobenzoic acid can be isolated. In the reaction the nitro group oxidizes the methyl side chain to carboxyl and is itself reduced to the amino group.

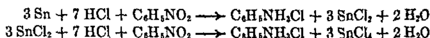
2. *Reduction to an aryl hydroxylamine.* Zinc dust under neutral conditions reduces nitrobenzene to phenylhydroxylamine.



$$C_6H_5NO_2 + 2\,Zn + 3\,H_2O \longrightarrow C_6H_5NHOH + 2\,Zn(OH)_2$$

An ammonium salt is added as a buffer to prevent the development of basicity. The reaction is used as a test for the nitro group because the aryl hydroxylamine rapidly reduces silver ion.

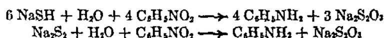
3. *Reduction to a primary amine.* This is the most important reaction of nitro compounds. In the laboratory the usual method is metallic tin and hydrochloric acid, or stannous chloride and hydrochloric acid. Stannous chloride reduces the *ortho*-nitro group in 2.4-dinitrobenzene first.



$$3\,Sn + 7\,HCl + C_6H_5NO_2 \longrightarrow C_6H_5NH_3Cl + 3\,SnCl_2 + 2\,H_2O$$
$$3\,SnCl_2 + 7\,HCl + C_6H_5NO_2 \longrightarrow C_6H_5NH_3Cl + 3\,SnCl_4 + 2\,H_2O$$

Other metals are used, for example, zinc and acetic acid (with hydrochloric acid chlorine enters the ring to some extent) or iron and hydrochloric acid. Industrially iron has been the reducing agent for decades; only one-fortieth of the theoretical amount of acid is needed.

Reduction can be effected by heating with a solution of ammonium hydrosulfide (NH_4HS) or sodium hydrosulfide (NaHS), preferably in alcohol, or of sodium disulfide (Na_2S_2).



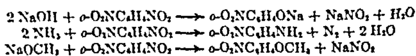
$$6\,NaSH + H_2O + 4\,C_6H_5NO_2 \longrightarrow 4\,C_6H_5NH_2 + 3\,Na_2S_2O_3$$
$$Na_2S_2 + H_2O + C_6H_5NO_2 \longrightarrow C_6H_5NH_2 + Na_2S_2O_3$$

Ammonium hydrosulfide usually does not reduce a nitro group *ortho* to some other group. Thus with 2,4-dinitrotoluene the result is different from that with stannous chloride (p. 479). Sodium sulfides may be used for reducing one nitro group of a dinitro compound, by taking the theoretical amount.

Industrially, reduction by hydrogen is preferred, because of ease of purification. The metallic catalyst is one not easily poisoned, for example, iron. With iron a temperature of 330 to 350° is needed.

4. *Reduction to azoxy, azo, and hydrazo compounds.* Depending upon the conditions and the strength of the reducing agent, alkaline reduction may yield one of a number of compounds in which two benzene rings are joined through nitrogen atoms. These are described in the succeeding section.

5. *Replacement of the nitro group.* A nitro group ordinarily is not easily replaced. It is activated by another nitro group, most when in the *ortho*-position, next in the *para*-, but hardly at all in the *meta*-position. In *o*-dinitrobenzene it is replaced by the hydroxyl group with sodium hydroxide, by amino with alcoholic ammonia, and by the methoxyl group with sodium methoxide.



$$2\,NaOH + o\text{-}O_2NC_6H_4NO_2 \longrightarrow o\text{-}O_2NC_6H_4ONa + NaNO_2 + H_2O$$
$$2\,NH_3 + o\text{-}O_2NC_6H_4NO_2 \longrightarrow o\text{-}O_2NC_6H_4NH_2 + N_2 + 2\,H_2O$$
$$NaOCH_3 + o\text{-}O_2NC_6H_4NO_2 \longrightarrow o\text{-}O_2NC_6H_4OCH_3 + NaNO_2$$

The last reaction takes place also with *p*-dinitrobenzene.

Nitrobenzene, $C_6H_5NO_2$. This is sometimes called oil of [illegible], [illegible] artificial oil of bitter almonds, which it resembles somewhat in [illegible]. It is [illegible] sparingly soluble in water and miscible in all proportions with [illegible] acid. Addition of water throws it out of solution largely. The main [illegible] benzene is in the manufacture of aniline. As a mild oxidizing [illegible] in the preparation of fuchsine and similar dyes and in the [illegible] (Chaps. 46 and 44).

Nitrotoluenes, $CH_3C_6H_4NO_2$. When toluene is nitrated with a mixture [illegible] and sulfuric acids, the product has about 55 per cent ortho-, 5 per [illegible]

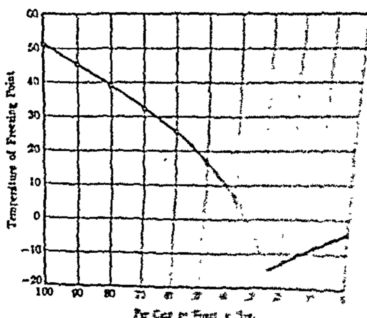
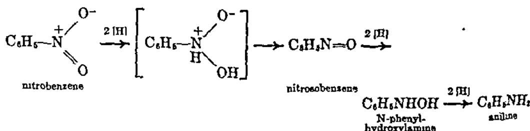


Figure 30 • Fusion Curve of Mixtures [illegible]

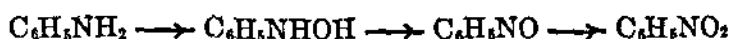
REDUCTION PRODUCTS OF NITROBENZENE

Reduction of nitrobenzene leads to a number of different compounds, the nature of the actual product depending upon the reducing agent and the acidity or alkalinity of the medium. The primary reduction products result from reaction in neutral or acidic solution. The stepwise reduction products can be thought of as resulting from the action of two atoms of hydrogen at each step. This is an old-fashioned approach, because actually the reduction is a taking on of electrons.



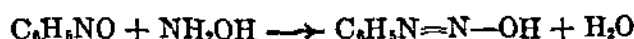
The loss of one oxygen atom or the gain of two hydrogen atoms constitutes a reduction step. Actually, the first reduction product that can be isolated is phenylhydroxylamine.

Nitrosobenzene, C_6H_5NO. This is not obtained by reducing nitrobenzene, because nitrosobenzene reduces more rapidly than does nitrobenzene. It can be obtained *by the oxidation of phenylhydroxylamine with dichromate and sulfuric acid,* or with peroxysulfuric acid (permonosulfuric acid, Caro's acid), H_2SO_5. Aniline also can be oxidized with the latter reagent, the oxidation proceeding through phenylhydroxylamine and continuing on to nitrobenzene. Yields usually are poor.



$$C_6H_5NH_2 \longrightarrow C_6H_5NHOH \longrightarrow C_6H_5NO \longrightarrow C_6H_5NO_2$$

Nitrosobenzene is a colorless solid having a disagreeable odor. It melts at 68° to an emerald-green liquid. The solid is readily soluble in benzene and other organic solvents to give green solutions immediately. The intense green color is characteristic of monomeric nitroso compounds. The solid is dimeric. Nitrosobenzene reacts with hydroxylamine, forming benzenediazohydroxide (p. 490).

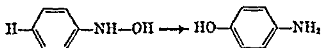


$$C_6H_5NO + NH_2OH \longrightarrow C_6H_5N{=}N{-}OH + H_2O$$

Two other reactions that are related to this one are those with N-phenylhydroxylamine and aniline (p. 465).

N-Phenylhydroxylamine, C_6H_5NHOH. This is obtained by reduction of nitrobenzene with zinc dust under neutral conditions (p. 462), and is the first oxidation product from the action of Caro's acid on aniline in ether at low temperatures. It is a colorless solid, m.p. 81.2°. Like hydroxylamine it is a strong reducing agent, reducing silver ion to metallic silver and Fehling's solution to cuprous oxide. *It is reduced* easily to aniline by stannous chloride, zinc and acetic acid, etc. It undergoes oxidation by the air, with formation of azoxybenzene and other products. It is unstable, slowly undergoing mutual oxidation and reduction. The first products, aniline and nitrosobenzene, react further and a variety of products result (p. 465).

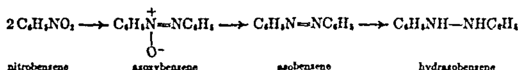
With dilute sulfuric acid phenylhydroxylamine undergoes a molecular rearrangement, in which the hydroxyl group migrates to the *para*-position on the benzene ring. The product is *p*-aminophenol.



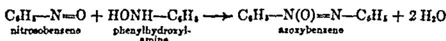
A similar type of reaction takes place with both *o*-tolyl- and *m*-tolylhydroxylamines and with other hydroxylamines in which the *para*-position is open.

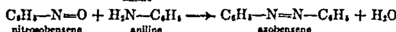
Rearrangement occurs with other types of compounds, also. An electronegative radical attached to a nitrogen atom on the benzene ring tends to migrate to the ring on the addition of acid. The *para*-position is taken preferably, and sometimes the *ortho*-position, when the *para* is occupied. In some cases even methyl groups migrate (p. 474).

Secondary Reduction Products. When nitrobenzene (other nitro compounds react similarly) is reduced under alkaline conditions with a not too vigorous reducing agent (zinc dust and alcoholic base), secondary reduction products are obtained, *viz.*, **azoxybenzene, azobenzene, and hydrazobenzene.**



These result from the primary reduction products by condensation reactions that can be carried out separately under alkaline conditions with the individual compounds.





The second reaction has been employed for the synthesis of many unsymmetrically substituted azobenzenes, starting with differently substituted nitrosobenzenes and anilines. A similar procedure, however, does not hold in the case of azoxybenzenes, for the products are mixtures of the possible symmetrical azoxybenzenes.

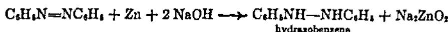
Azoxybenzene is obtained most easily by heating nitrobenzene with methanolic sodium (or potassium) hydroxide, a mild reducing agent.



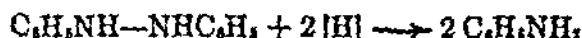
Azobenzene is easily obtained from nitrobenzene by heating with metallic magnesium, or from azoxybenzene by adding iron filings and distilling.



Hydrazobenzene is obtained by reduction of azobenzene with zinc dust and alcoholic sodium hydroxide.

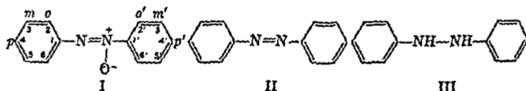


Azoxybenzene, azobenzene, and hydrazobenzene are solids (m.p. 36°, 69°, and 131°, respectively) and are insoluble in water, dilute aqueous bases, or acids. (Hydrazobenzene, however, rearranges with acids. With zinc and acetic acid or with any other active reducing agents the nitrogen-to-nitrogen bond is cleaved and the compounds are reduced to aniline. The reduction probably proceeds in steps through hydrazobenzene.



$$C_6H_5NH—NHC_6H_5 + 2\,[H] \longrightarrow 2\,C_6H_5NH_2$$

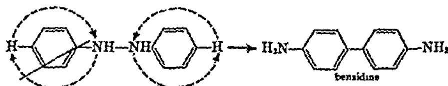
The compounds are interesting because of their color. Azoxybenzene, I, is orange; azobenzene, II, is red, and hydrazobenzene, III, is colorless. It can be seen from the respective formulas that in I and II there is a completely conjugated system of single and double bonds, but in III the single bond between nitrogen atoms breaks the conjugation.



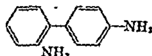
The conjugated system of I or II is believed to be the cause of color. Azoxybenzene and, in particular, azobenzene are the parent substances of large numbers of valuable dyes, *viz*, the azoxy and azo dyes (Chap. 46). The numbering of the rings starts at the nitrogen atom. Primed numbers or letters apply to the other ring.

Hydrazobenzene (also other similar hydrazo compounds) is colorless when pure but rapidly becomes red on exposure to air through oxidation of hydrazobenzene to azobenzene by oxygen. Hydrogen peroxide is formed at the same time. Hydrazobenzene is unstable in contact with strong mineral acids and rearranges to benzidine.

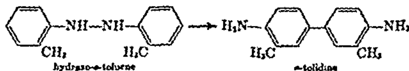
The Benzidine Rearrangement. Hydrazobenzene in contact with acids (dilute aqueous acids or a hydrogen halide in an inert solvent) undergoes an intramolecular rearrangement. The principal reaction product is benzidine (*p,p'*-diaminobiphenyl).



This change involves the simultaneous migration of two groups, from a nitrogen atom to the *para*-position on the benzene ring. A less important product is *o,p'*-diaminobiphenyl,



When hydrazo-*o*-toluene (*o,o'*-dimethylhydrazobenzene) undergoes the change, the relative positions of the carbon and nitrogen atoms remain the same in the product, 3,3'-dimethyl-4,4'-diaminobiphenyl (*o*-tolidine).



The corresponding *p,p'*-dimethylhydrazobenzene undergoes the semidine rearrangement. The product, 6-amino-3,4'-dimethyldiphenylamine, is a derivative of diphenylamine (p. 476) rather than one of biphenyl (p. 517). The name "semidine" signifies that this rearrangement involves only half of the migrations of the benzidine rearrangement.

Identification of Nitro Compounds. Aromatic nitro compounds, unless they have also an amino, hydroxy, carboxyl, or sulfonic acid group are insoluble in water and in aqueous acids or bases. Nitro compounds dissolve in cold, concentrated sulfuric acid and may be precipitated out unchanged on the addition of water, except in those cases where sulfonation proceeds rapidly (phenols). Nitro compounds may be detected by heating the substance with zinc dust, ammonium nitrate, and water, filtering, and adding a few drops to aqueous silver nitrate. Reduction indicates a nitro (or nitroso) compound which was reduced to the hydroxylamine stage. When the nitro compound is insoluble in water, it will dissolve when added to tin and hydrochloric acid, owing to the formation of an amine salt. Stannous chloride in hydrochloric acid may be used instead of the tin. Addition of a strong base liberates the amine. By establishing the identity of this amine the identification of the original nitro compound may be made complete.

PROBLEMS

1. Starting with benzene and any aliphatic compound and assuming that a solid *para*-sulfonic acid can be separated satisfactorily from an *ortho,para*-mixture resulting from direct sulfonation, show the steps and conditions for the reactions involved in a practical preparation of the following, and write equations with the actual reactants:

a) *m*-bromobenzenesulfonyl chloride
b) *p*-bromobenzenesulfonyl chloride
c) *m*-chlorobenzenesulfonamide
d) *p*-chlorobenzenesulfonamide
e) N-methylbenzenesulfonamide
f) *m*-bromobenzenesulfonamide
g) *p*-bromo-N,N-dimethylbenzenesulfonamide
h) sodium *p*-bromo-N-chlorobenzenesulfonamide
i) *m*-bromo-N-methylbenzenesulfonamide
j) *p*-chloro-N,N-dimethylbenzenesulfonamide
k) *m*-bromo-N-methylbenzenesulfonamide
l) *p*-ethylbenzenesulfonyl chloride
m) *p*-isopropylbenzenesulfonamide
n) *p*-isopropyl-N-methylbenzenesulfonamide
o) *o*-chlorotoluene-*p*-sulfonyl chloride
p) *m*-sulfobenzoic acid
q) *o*-chloroethylbenzene-*p*-sulfonyl bromide
r) *p*-hydroxyethylbenzene
s) *p*-cyanoethylbenzene
t) *p*-ethylbenzoic acid
u) terephthalic acid
v) α-chlorotoluene-*p*-sulfonyl chloride
w) *o*-chlorotoluene-*p*-sulfonyl chloride
x) *o*-nitrotoluene-*p*-sulfonyl chloride

2. Starting with toluene and any aliphatic compound and assuming that a solid *para*-isomer can be obtained pure from an *ortho,para*-mixture, show the sequence of reactions (reactants and conditions) for a practical preparation of:

a) *p*-toluenesulfonic acid
b) *p*-toluenesulfonyl chloride
c) p-cyanotoluene
d) *p*-cresol
e) *p*-toluenesulfonamide
f) p-toluene-N-ethylsulfonamide
g) *p*-toluene-N,N-diethylsulfonamide
h) *o*-bromotoluene-*p*-sulfonyl chloride
i) sodium *o*-bromotoluene-*p*-N-bromosulfonamide
j) *p*-sulfobenzyl chloride
k) *p*-bromotoluene-*o*-sulfonic acid
l) *p*-toluene-N-*n*-propylsulfonamide
m) sodium *o*-chlorotoluene-*p*-N-methylsulfonamide
n) *o*-bromotoluene
o) *o*-chlorotoluene
p) toluene-2,4-disulfonic acid
q) *p*-methylbenzoic acid
r) *m*-sulfo-*p*-bromobenzoic acid
s) *o*-methylbenzoic acid
t) *o*-bromotoluene-*p*-N,N-dimethylsulfonamide

3. Show a practical laboratory preparation of the following, reasonably free of isomeric forms, from any aliphatic compound and toluene.

a) *o*-methyl-N-phenylhydroxylamine
b) *p*-methyl-N-phenylhydroxylamine
c) *o*-nitrobenzoic acid
d) *p,p'*-dimethylazobenzene
e) *o*-nitrobenzyl chloride
f) *p*-nitrobenzoic acid
g) *o,o'*-dimethylazobenzene
h) *n*-propyl *p*-nitrobenzoate
i) *o,o'*-dimethylhydrazobenzene
j) *p,p'*-dimethylhydrazobenzene
k) potassium *p*-nitrotoluene-*o*-sulfonate
l) *o*-bromo-*p*-nitrotoluene
m) *n*-butyl *o*-nitrobenzoate
n) *p*-nitrobenzyl chloride
o) *o*-nitrosotoluene
p) 3-nitro-4-bromobenzoic acid
q) *o,p'*-dimethylazobenzene
r) 2-chloro-4,2'-dimethylazobenzene
s) *o,p'*-dimethylhydrazobenzene
t) *o*-amino-*p*-sulfotoluene

4. Describe a convenient chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) sodium *p*-chlorobenzenesulfonamide and sodium N-chlorobenzenesulfonamide
b) N-ethyl-*p*-toluenesulfonamide and N,N-dimethyl-*p*-toluenesulfonamide
c) *p*-chlorobenzenesulfonic acid and benzenesulfonyl chloride
d) ethyl *p*-bromobenzenesulfonate and *p*-ethylbenzenesulfonyl bromide
e) *p*-bromobenzene-N-ethylsulfonamide and *p*-ethylbenzene-N-bromosulfonamide
f) *o*-bromobenzenesulfonamide and *o*-nitrobenzenesulfonyl bromide
g) methyl benzenesulfonate and *p*-toluenesulfonic acid
h) *p*-chlorobenzenesulfonamide and N,N-dimethyl-*p*-chlorobenzenesulfonamide
i) methyl *p*-bromobenzenesulfonate and *p*-toluenesulfonyl bromide
j) *o*-nitrotoluene and *p*-nitrotoluene
k) *p*-nitrotoluene and nitrobenzene
l) 2-bromo-4-nitrotoluene and 3-bromo-4-nitrotoluene
m) *p*-nitrophenol and N-phenylhydroxylamine
n) *p*-nitrotoluene and *p*-nitrosotoluene
o) *p*-nitrotoluene and *α*-nitrotoluene

p) *p*-nitrotoluene and 2,4-dinitrotoluene
q) *p*-nitrotoluene and N-phenylhydroxylamine
r) *p-nitrotoluene and hydrazobenzene*
s) azobenzene and azoxybenzene
t) hydrazobenzene and N-phenylhydroxylamine

5. Describe a procedure for making a convenient, quantitative separation of the following two substances from each other and for recovering at least one component reasonably quantitatively.

a) *p*-toluenesulfonamide and N,N-dimethyl-*p*-toluenesulfonamide
b) N-*n*-butylsulfonamide and N,N-diethylbenzenesulfonamide
c) sodium *p*-ethylbenzenesulfonate and sodium N-ethylbenzenesulfonamide
d) *m*-xylene-4-sulfonyl chloride and 3-chlorotoluene-4-sulfonic acid
e) *m*-bromobenzenesulfonamide and *m*-bromobenzenesulfonic acid
f) *p*-toluenesulfonic acid and N-methylbenzenesulfonamide
g) *m*-dinitrobenzene and *m*-nitrobenzenesulfonamide
h) *o*-nitrotoluene and *m*-nitrobenzenesulfonamide
i) *o*-dibromobenzene and *o*-nitrotoluene
j) 2,4-dibromotoluene and *p*-nitrotoluene
k) durene and nitrobenzene
l) *o*-nitrotoluene and α-nitrotoluene

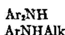
CHAPTER 31

Aromatic Amines

There are two groups of amines derived from aromatic hydrocarbons, *viz.*, the aryl amines, in which the nitrogen atom is attached to nuclear carbon, and the aralkyl amines, in which it is attached to a carbon atom of a side chain. The latter group, of which benzylamine, $C_6H_5CH_2NH_2$, is a typical example, are aliphatic amines and undergo the characteristic reactions of these amines. This chapter is concerned with the true aryl amines, of which aniline, $C_6H_5NH_2$, is the simplest example. They resemble the aliphatic amines in a number of respects. Primary aryl amines are distinguished from the alkyl amines in that they form diazonium salts easily.

Types of Aryl Amines. Like the aliphatic amines there are three classes, *viz.*, primary, secondary, and tertiary; these may be divided into the following types, in which Alk represents an alkyl radical and Ar an aryl radical. The two most important types are underlined.







primary secondary tertiary

Preparation of Amines. 1. *Primary Amines*, $ArNH_2$. The principal method of preparation is reduction of the corresponding nitro compound (p. 462). Although aryl halides are unreactive under ordinary conditions, an important industrial process is the reaction of chlorobenzene with ammonia at 200° in the presence of cuprous oxide (p. 452). Primary amines can be obtained by degradation of amides and azides (pp. 374, 375).

Recovery of the amine from the mixture resulting from the reduction of a nitro compound with a metal whose hydroxide is insoluble in aqueous base (tin, iron), usually is accomplished by steam distillation from an alkaline solution. If the hydroxide is soluble in aqueous base (zinc) or if the oxidation product of the reducing agent is soluble in aqueous base (sodium bisulfite from sodium hydrosulfite, phosphorous acid from hypophosphorous acid), the amine can be extracted with ether from a basic solution.

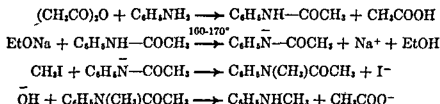
2. *Secondary amines*, ArNHAlk. These are obtained by the reaction of primary amines with alkylating agents, for example, alkyl halides, alkyl sul-

fates, alkyl sulfonates, etc. Dimethyl sulfate reacts well when in contact with cold water.



$$(CH_3)_2SO_4 + C_6H_5NH_2 \longrightarrow C_6H_5NHCH_3 + CH_3OSO_2OH$$

Since tertiary amines also may be formed, it often is necessary to effect separation. A secondary amine can be obtained free of tertiary amine from an amide of the primary aromatic amine, for example, acetanilide, by first converting it to a metallic salt, alkylating, and then hydrolyzing.



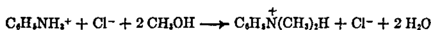
$$(CH_3CO)_2O + C_6H_5NH_2 \longrightarrow C_6H_5NH{-}COCH_3 + CH_3COOH$$

$$EtONa + C_6H_5NH{-}COCH_3 \xrightarrow{100\text{-}170°} C_6H_5\bar{N}{-}COCH_3 + Na^+ + EtOH$$

$$CH_3I + C_6H_5\bar{N}{-}COCH_3 \longrightarrow C_6H_5N(CH_3)COCH_3 + I^-$$

$$\bar{O}H + C_6H_5N(CH_3)COCH_3 \longrightarrow C_6H_5NHCH_3 + CH_3COO^-$$

3. *Tertiary amines*, $ArNAlk_2$. Alkylating agents in excess convert primary and secondary amines to tertiary amines; an industrial method for dimethylaniline involves heating aniline hydrochloride and methanol at 235°.



$$C_6H_5NH_3^+ + Cl^- + 2\,CH_3OH \longrightarrow C_6H_5\overset{+}{N}(CH_3)_2H + Cl^- + 2\,H_2O$$

However, with the proper amount of alcohol and at a lower temperature, methylaniline is the main product.

Properties of Amines. As compared to the simpler aliphatic amines, the aromatic amines have higher melting and boiling points and lower solubilities in water (Table 86).

TABLE 86 | **Some Aromatic Amines**

NAME	FORMULA	M.P. °C	B.P. °C	SP. GR. 20°/4°	SOLY. IN H_2O G./100 G	K_b
Aniline	$C_6H_5NH_2$	−6.0	184.4	1.0217	3.7	4.2×10^{-10}
N-Methylaniline	$C_6H_5NHCH_3$	−57	196.1	0.989	v.s.sol.	7.1×10^{-10}
N,N-Dimethylaniline	$C_6H_5N(CH_3)_2$	2.5	193.5	0.956	1.4	1.1×10^{-9}
Diphenylamine	$(C_6H_5)_2NH$	53.10	302	1.16	0.003	7×10^{-14}
Triphenylamine	$(C_6H_5)_3N$	127	365	0.774	insol.	
o-Toluidine	$1,2\text{-}CH_3C_6H_4NH_2$	−27.7	199.8	0.9984	1.7	2.5×10^{-10}
m-Toluidine	$1,3\text{-}CH_3C_6H_4NH_2$	−30.4	203.3	0.9889	s. sol.	4.9×10^{-10}
p-Toluidine	$1,4\text{-}CH_3C_6H_4NH_2$	43.6	200.4	1.046	0.74	1.2×10^{-9}
Benzylamine	$C_6H_5CH_2NH_2$		184.5	0.981	misc.	2.3×10^{-5}
o-Phenylenediamine	$1,2\text{-}C_6H_4(NH_2)_2$	103.8	252		3	3.2×10^{-10}
m-Phenylenediamine	$1,3\text{-}C_6H_4(NH_2)_2$	62.8	237		25	7.6×10^{-10}
p-Phenylenediamine	$1,4\text{-}C_6H_4(NH_2)_2$	142[a]	267		3.8	1.1×10^{-8}

[a] m.p. of dihydrate, 82°.

A comparison of the K_b of ammonia (1.8×10^{-5}) with that of aniline shows that the phenyl group has a strongly depressing influence upon the basic ion-

ization when it is linked to the nitrogen atom of the amino group. Diphenylamine is such a weak base that its hydrochloride, formed when dry hydrogen chloride is passed into an ether solution of diphenylamine, is completely hydrolyzed by water. When the phenyl group is separated from the nitrogen atom by a carbon atom, as in benzylamine, it has only a slight influence upon the basicity. The phenyl group increases acidity, for diphenylamine forms a potassium salt when heated with metallic potassium at 100°.

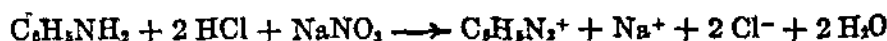
Reactions of Primary Amines. These may involve the amino group or the benzene ring. It will be recalled that the benzene ring is markedly activated by the amino group (p. 441). The first three reactions below are also those of aliphatic amines.

1. *Basic properties; coordination with a proton.* Although aniline and other aryl amines are much weaker bases than ammonia and aliphatic amines, with strong acids they form salts that are stable in aqueous solution.

2. *Alkylation.* Alkylating reagents give monoalkyl and dialkylanilines with aniline and similar compounds with other amines.

3. *Acylation.* Aniline and other primary amines react with acyl halides, anhydrides, isocyanates, sulfonyl halides, etc. (pp. 356, 458).

4. *Diazotization.* When an amine salt reacts with hydrochloric acid and sodium nitrite at 0 to 10°, a diazonium salt is formed.



$$C_6H_5NH_2 + 2\,HCl + NaNO_2 \longrightarrow C_6H_5N_2^+ + Na^+ + 2\,Cl^- + 2\,H_2O$$

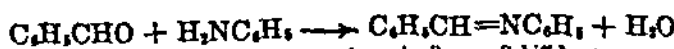
It will be recalled that an aliphatic primary amine yields an alcohol, nitrogen, and water (p. 357). Benzylamine reacts as an aliphatic amine. When an aqueous solution of the diazonium salt is heated, nitrogen is eliminated and the corresponding hydroxy compound, phenol, is formed.



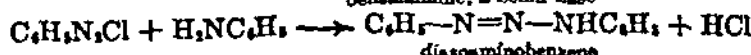
$$C_6H_5N_2^+ + Cl^- + H_2O \longrightarrow C_6H_5OH + N_2 + HCl$$

Diazonium compounds undergo a large number of reactions and constitute one of the most important groups of aromatic compounds (Chap. 32).

5. *Condensation at the amino group.* A number of reactions take place at the amino group, similar to those with aliphatic primary amines. Some reactive substances are chloroform, forming isocyanides, phosgene, forming isocyanates, and carbon bisulfide, forming isothiocyanates (pp. 358, 359). Two other interesting reactions are those with aldehydes, yielding Schiff bases, and those with diazonium salts, yielding diazoamino compounds (p. 488).

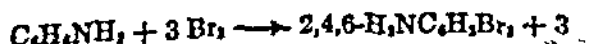


$$C_6H_5CHO + H_2NC_6H_5 \longrightarrow \underset{\text{benzalaniline; a Schiff base}}{C_6H_5CH{=}NC_6H_5} + H_2O$$



$$C_6H_5N_2Cl + H_2NC_6H_5 \longrightarrow \underset{\text{diazoaminobenzene}}{C_6H_5{-}N{=}N{-}NHC_6H_5} + HCl$$

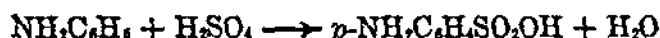
6. *Substitution reactions.* Aryl amines undergo substitutions with great ease. As an example, aniline in aqueous solution reacts very rapidly with aqueous bromine and is converted into insoluble tribromoaniline.



$$C_6H_5NH_2 + 3\,Br_2 \longrightarrow 2,4,6\text{-}H_2NC_6H_2Br_3 + 3$$

The reaction cannot be controlled in aqueous solution to give monobromoaniline because subsequent reactions also take place. But in glacial acetic acid the reaction proceeds stepwise so that monobromination can be realized. Chlorination proceeds similarly to bromination. Sulfonation and nitration are different, because of salt formation; moreover, nitric acid may react oxidatively, forming oxides of nitrogen, which in turn may bring about diazotization; the overall result sometimes is a black, tarry mass.

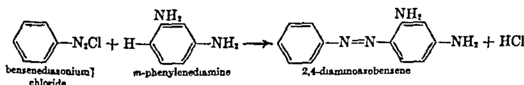
Sulfonation is accomplished by heating aniline and concentrated sulfuric acid for many hours at 180°. The product is sulfanilic acid, *p*-sulfoaniline.



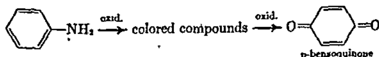
$$NH_2C_6H_5 + H_2SO_4 \longrightarrow p\text{-}NH_2C_6H_4SO_2OH + H_2O$$

Nitration can be accomplished with little or no oxidation if the reaction is carried out in a large amount of concentrated sulfuric acid; the product is a mixture of the *meta*- and *para*-isomers. In general, it is preferable to "protect" the amino group by acetylation to acetanilide; this is then smoothly nitrated, without oxidation, to nitroacetanilide (Table 81, p. 437).

7. *Condensation on the ring.* When a position on the ring is extremely reactive, for example, when two activating groups reinforce each other, or when a dialkylamino group is attached to the ring (p. 475), diazo coupling takes place directly on the ring.



8. *Oxidation.* Aniline undergoes two types of oxidation. Hydrogen peroxide and Caro's acid (monoperoxysulfuric acid, H_2SO_5) give phenylhydroxylamine, nitrosobenzene, nitrobenzene, *p*-benzoquinone, and some secondary products formed by interactions of the primary products (p. 465). These reagents oxidize by adding oxygen. Chromic acid and diperoxysulfuric acid, $H_2S_2O_8$, oxidize by taking hydrogen from the amino group. The reaction products are complicated in structure, and many are highly colored (emeraldine, nigraniline). From them useful dyes are manufactured (aniline black), and from them *p*-benzoquinone is obtained by further action of the oxidizing agent.



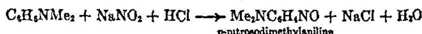
When a mixture of aniline with either *o*- or *p*-toluidine is oxidized with the proper mild oxidizing agent (lead dioxide, arsenic acid, or nitrobenzene), an intensely colored reddish dye is obtained. A similar dye is obtained from *o*- or *p*-toluidine alone, or from a mixture of the two. These are triphenylmethane dyes, for example, rosaniline and pararosaniline (Chap. 46).

Reactions of Secondary and Tertiary Amines. These resemble primary amines in their basic properties and in substitution reactions. They differ in their reaction with nitrous acid and in the stability of their hydrochlorides when heated. Tertiary amines differ also in that condensation reactions take place only on the ring. The *para*-position is much more reactive than the *ortho*-.

Nitrous acid forms N-nitrosoamines with secondary, and *p*-nitroso derivatives with tertiary amines.

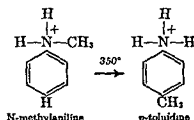


$$C_6H_5NHMe + NaNO_2 + HCl \longrightarrow \underset{\text{methylaniline nitrosoamine}}{C_6H_5N(NO)Me} + NaCl + H_2O$$

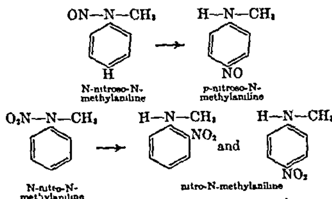


$$C_6H_5NMe_2 + NaNO_2 + HCl \longrightarrow \underset{p\text{-nitrosodimethylaniline}}{Me_2NC_6H_4NO} + NaCl + H_2O$$

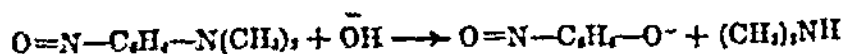
Secondary amines undergo rearrangement when their hydrochlorides are heated sufficiently (about 350° in sealed tubes), provided the *para*-position is open.



Other compounds also rearrange, some more easily than the N-methyl derivatives. Negative radicals migrate more readily than methyl, for example, nitroso and nitro migrate when the compounds are heated with aqueous acid.

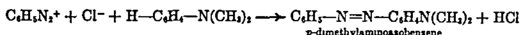


Nitroso derivatives of tertiary amines are useful in the preparation of pure secondary aliphatic amines, for they are decomposed when heated with dilute aqueous sodium hydroxide. Thus *p*-nitrosodimethylaniline yields dimethylamine.



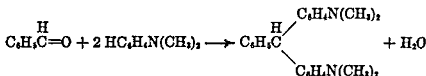
$$O{=}N{-}C_6H_4{-}N(CH_3)_2 + \overset{-}{O}H \longrightarrow O{=}N{-}C_6H_4{-}O^- + (CH_3)_2NH$$

Tertiary amines react with diazonium salts (p. 488). Coupling takes place on the ring, preferably at the *para*-position and if this is occupied, at the *ortho*-.



$$C_6H_5N_2^+ + Cl^- + H{-}C_6H_4{-}N(CH_3)_2 \longrightarrow \underset{p\text{-dimethylaminoazobenzene}}{C_6H_5{-}N{=}N{-}C_6H_4N(CH_3)_2} + HCl$$

Aldehydes and ketones react when heated with a suitable catalyst (zinc chloride). Benzaldehyde is one of the best examples.



$$C_6H_5\overset{H}{C}{=}O + 2\,HC_6H_4N(CH_3)_2 \longrightarrow C_6H_5\overset{H}{C}(C_6H_4N(CH_3)_2)_2 + H_2O$$

The product, *p,p'*-bis-dimethylaminotriphenylmethane, is a step in the manufacture of malachite green (Chap. 46).

Mutual Influence of the Amino Group and the Nucleus upon Each Other. The benzene ring decreases the basicity and increases the acidity of the amino group. It modifies the reaction of primary amines with nitrous acid to such an extent that the diazonium compounds are stable On the other hand, the amino group increases the ease with which the molecule undergoes oxidation, substitution, and condensation. The reactions of dimethylaniline illustrate the activating effect of the dimethylamino group, $N(CH_3)_2$, upon the *para*-position and the ease with which condensation takes place there.

Molecular Rearrangements. When different radicals are attached to the nitrogen atom in aniline or its homologs, these will under the proper conditions migrate to the *para*- or *ortho*-position in the benzene ring and thus bring about a rearrangement of the atoms in the molecule with the production of an isomeric compound. The more electronegative the radical, the more easily the rearrangement takes place; for example, the sulfo and nitro groups migrate in the cold to the *ortho*-position on the addition of any strong acid; nitroso, hydroxyl, and phenylamino migrate to the *para*-position almost as easily, while methyl in the hydrochloride migrates only at high temperatures. All of these changes, none of which are reversible, involve an increase in bond energies. In each case the final product is the more stable of the two isomers.

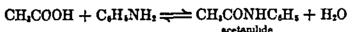
Aniline, $C_6H_5NH_2$. This was first obtained (1828) by heating indigo (Sp , *anil*, indigo). It is a colorless liquid that slowly darkens on standing, owing mainly to oxidation to highly colored compounds. Aniline, although but slightly soluble in water (Table 86) dissolves readily in aqueous acids. Aniline hydrochloride, $C_6H_5NH_3Cl$, is soluble 107 g. per 100 g. of water at 25°. The sulfate, $(C_6H_5NH_3)_2SO_4$, is much less soluble, 5 g. per 100 g. In general, sulfates of amines are much less soluble than chlorides.

For laboratory preparation of aniline from nitrobenzene the usual reducing agent is metallic tin and hydrochloric acid (p. 462). In industry the reduction is catalytic hydrogenation of nitrobenzene or ammonolysis of chlorobenzene (p. 452). For many decades the method was reduction of nitrobenzene by heating with iron, water, and

An interesting group of quaternary ammonium compounds are those having a long aliphatic chain of ten to sixteen carbon atoms. These, like soaps, have detergent properties but, unlike soaps, the detergent properties reside in the cation, not the anion. They have been called **invert soaps.** They are effective in salt solutions and also in acid solutions. Many have bactericidal properties.

ACYL DERIVATIVES

The acylation of primary and secondary amines, like that of aliphatic amines (p. 356), is conveniently done with an anhydride or acyl halide. If with the latter, an inorganic base or tertiary amine should also be present, otherwise only part of the primary or secondary amine is acylated. This is especially desirable with sulfonyl halides. These are the conditions under which the Hinsberg test for amines is carried out (p. 458). The products formed are sulfonamides. For large scale preparation of amides of carboxylic acids, as in the preparation of acetamide, heating the amine with an excess of the acid and removing the water as it is formed by distillation of aqueous acid displaces the position of equilibrium and allows the reaction to be carried to completion.

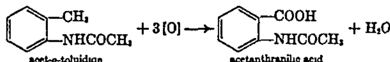


$$CH_3COOH + C_6H_5NH_2 \rightleftharpoons \underset{\text{acetanilide}}{CH_3CONHC_6H_5} + H_2O$$

The acyl group can be removed by hydrolysis. Those of carboxylic acids are removed either by acidic or basic hydrolysis, those of sulfonic acids by acidic hydrolysis. Thus after a radical has served some purpose, more particularly to protect the amino group, it can be removed so as to regenerate the original basic group.

The names of acyl derivatives usually end in -ide to indicate their amide structure. Acetylated aniline, $CH_3CONHC_6H_5$ is acetanilide, and the benzenesulfonyl derivative of *p*-toluidine is benzenesulfon-*p*-toluidide.

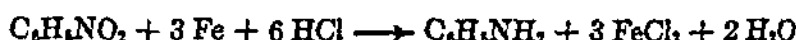
Protecting the Amino Group. For a number of reactions a free amino or alkylamino group is undesirable, because either salt formation or undesirable oxidation may take place. Salt formation may be undesirable in substitution reactions (p 436) and unwanted oxidation may accompany halogenation or nitration of the ring or oxidation of a side chain. Acylation (usually acetylation) greatly diminishes the unwanted reactions. Amides are such weak acids (Table 86) that only a fraction is converted to a salt under ordinary conditions. Thus the product from nitration, sulfonation, bromination, etc., is an *ortho,para*-mixture, rather than the *meta*-isomer. Oxidation of side chains is also possible, for example, acet-*o*-toluidide can be oxidized to acetanthranilic acid with neutral permanganate.



Thus anthranilic acid can be obtained from the acetyl derivative by hydrolysis, but if *o*-toluidine were oxidized, the reaction would take an entirely different course.

Acetanilide, N-Phenylacetamide, $CH_3CONHC_6H_5$. This is easily prepared by the method just mentioned. It is a neutral solid (Table 87). It undergoes substitution easily; in aqueous solution it yields the *para*-derivatives with chlorine and with bromine water; in acetic acid, mixtures of *ortho* and *para*. Nitration with nitration mixture gives mainly *p*-nitroacetanilide (Table 87) and with acetyl nitrate, CH_3COONO_2, in carbon tetrachloride, mainly *o*-nitroacetanilide (Table 87). Acet-

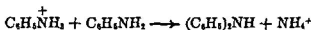
hydrochloric acid, the latter in amount only about one fortieth that needed to convert the iron to iron chloride.

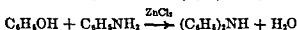


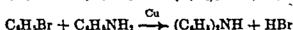
The reaction is catalyzed by the dissolved iron chlorides. Because of the deficiency of acid, the iron is converted mainly to magnetic oxide, Fe_3O_4. Aniline is an important intermediate in the manufacture of numerous dyes and of many other aromatic compounds.

Dimethylaniline, $C_6H_5N(CH_3)_2$. This is manufactured on a large scale by heating aniline hydrochloride with methanol under pressure (p. 472). Like aniline, it is colorless but darkens on exposure to air. It is an important intermediate in dye chemistry.

Diphenylamine, $(C_6H_5)_2NH$. This is obtained by heating under pressure a mixture of aniline and aniline hydrochloride at 210 to 240° for several hours, of aniline and phenol with zinc chloride or antimony trichloride, or of aniline and bromobenzene with finely divided copper in boiling nitrobenzene (200–220°).







These and other methods can be applied to homologs of diphenylamine.

Two interesting reactions of diphenylamine are those with bases and with oxidizing agents. The amine is both weakly acidic and basic (Table 86) and forms a sodium salt when heated with sodamide.



When an oxidizing agent in small amount is added to a solution of diphenylamine in concentrated sulfuric or phosphoric acid, an intense blue color develops. This is believed to be a salt of a free radical related to N,N'-diphenylbenzidine.



(Chap. 37). Among the oxidizing agents that react are oxygen, nitrate, nitrite, dichromate, permanganate, bromate, iodate, and ferric ion. The amine can serve as an indicator in titrations of ferrous iron with dichromate or in other oxidation reactions. Diphenylamine is used as a stabilizer for nitroglycerine.

Quaternary Ammonium Compounds. The starting materials for a quaternary ammonium compound usually are benzyl chloride and an aliphatic tertiary amine. These react readily to yield a quaternary ammonium salt.



Such a salt can be converted to the corresponding strong quaternary ammonium base by sodium hydroxide in alcohol, because of the low solubility of sodium chloride in alcohol.



An interesting group of quaternary ammonium compounds are those having a long aliphatic chain of ten to sixteen carbon atoms. These, like soaps, have detergent properties but, unlike soaps, the detergent properties reside in the cation, not the anion. They have been called **invert soaps.** They are effective in salt solutions and also in acid solutions. Many have bactericidal properties.

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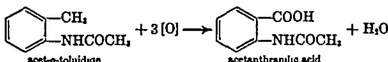


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The acyl group can be removed by hydrolysis. Those of carboxylic acids are removed either by acidic or basic hydrolysis, those of sulfonic acids by acidic hydrolysis. Thus after a radical has served some purpose, more particularly to protect the amino group, it can be removed so as to regenerate the original basic group.

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anilide is used in medicine as an antipyretic under the name "Antifebrin" and is a starting material in the preparation of many sulfa drugs, including sulfanilamide, sulfaguanidine, sulfathiazole, etc. (Chap. 45).

Acettoluidides, N-Acetyltoluidines, $CH_3CONHC_6H_4CH_3$. These are obtained from the corresponding toluidines by acetylation.

TABLE 87 | Some Substituted Anilines

NAME	FORMULA	M.P. °C	B.P. °C	SOLY. IN H_2O g./100 g. 20°	K_b
o-Chloroaniline	1,2-$NH_2C_6H_4Cl$	−1.94	208.8	0.9 [a]	5×10^{-12}
m-Chloroaniline	1,3-$NH_2C_6H_4Cl$	−10.4	236.5	0.6 [b]	3×10^{-11}
p-Chloroaniline	1,4-$NH_2C_6H_4Cl$	69.7	232.3	0.5 [c]	1.5×10^{-10}
o-Nitroaniline	1,2-$NH_2C_6H_4NO_2$	71.5	166 [e]	0.12	3.5×10^{-14}
m-Nitroaniline	1,3-$NH_2C_6H_4NO_2$	114	305–307 [d]	0.09	3.2×10^{-12}
p-Nitroaniline	1,4-$NH_2C_6H_4NO_2$	147.8	332	0.05	1×10^{-13}
Orthanilic acid	1,2-$NH_2C_6H_4SO_3H$			1.0	
Metanilic acid	1,3-$NH_2C_6H_4SO_3H$			2	
Sulfanilic acid [f]	1,4-$NH_2C_6H_4SO_3H$			1	1.6×10^{-12}
Acetanilide	$CH_3CONHC_6H_5$	114.25	305	0.54	4.4×10^{-14}
o-Nitroacetanilide	1,2-$AcNHC_6H_4NO_2$	93		0.22	
m-Nitroacetanilide	1,3-$AcNHC_6H_4NO_2$	154.5			
p-Nitroacetanilide	1,4-$AcNHC_6H_4NO_2$	215.9		0.22	
Acet-*o*-toluidide	1,2-$AcNHC_6H_4CH_3$	112	296	0.86	
Acet-*m*-toluidide	1,3-$AcNHC_6H_4CH_3$	66.5	303	0.8	
Acet-*p*-toluidide	1,4-$AcNHC_6H_4CH_3$	153	306	1.2	

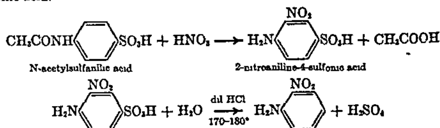
[a] At 71°. [b] At 75°. [c] At 42°. [d] Decomposing. [e] At 28 mm. [f] $K_a = 2.8 \times 10^{-3}$.

SUBSTITUTED ANILINES

There are many known derivatives of aniline in which one or more substituents are attached to the benzene ring. A number of these are listed in Table 87.

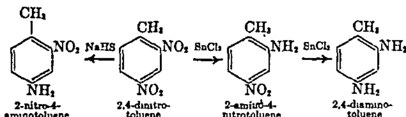
Electronegative radicals (nitro, chloro, etc.) decrease the basic constant of aniline. In general, the effect is greatest in the *ortho*-, next in the *para*-, and least in the *meta*-position. The anilinesulfonic acids are strong acids.

Nitroanilines, Nitranilines, $H_2NC_6H_4NO_2$. Of these the *meta*-isomer is most readily prepared since it is obtained by the reduction of *m*-dinitrobenzene with ammonium sulfide The *para*-isomer, from *p*-nitroacetanilide (see above) by hydrolysis, is also easily prepared, and the *ortho*-isomer is available from the nitration of N-acetylsulfanilic acid.



In the nitration reaction the nitro group enters the *ortho*-position because the *para*-position is blocked.

Nitrotoluidines, $CH_3C_6H_3(NH_2)NO_2$. The most interesting are those from 2,4-dinitrotoluene. This can be reduced stepwise; when the reducing agent is the calculated amount of stannous chloride with hydrochloric acid in alcoholic solution, the *o*-nitro group is reduced, and when it is sodium hydrosulfide in alcohol or ammonium sulfide in cold alcohol, the *p*-nitro group is reduced. The two different compounds are useful in the synthesis of numerous derivatives of toluene.



An excess of stannous chloride and hydrochloric acid reduces both compounds to 2,4-diaminotoluene.

Sulfanilic Acid, *p*-Sulfoaniline, 1,4-$NH_2C_6H_4SO_3H$. This is the most important of the anilinesulfonic acids. It is obtained by heating aniline and sulfuric acid for several hours in a bath at 180 to 190°. The *ortho*- and *meta*-isomers are obtained by reducing the corresponding nitrobenzenesulfonic acids.

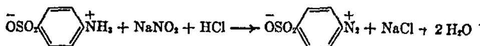
Sulfanilic acid is a strong acid and a weak base (Table 87) and exists as an inner salt or dipolar ion, $^{+}H_3NC_6H_4SO_3^{-}$ (p. 582). It is only slightly soluble in water and in dilute aqueous acids, readily soluble in aqueous bases or carbonates. It is even less soluble in alcohol and ether. The low solubility of such a relatively simple substance in alcohol and ether indicates a saltlike nature.

Nitric acid converts sulfanilic acid into 2,4-dinitraniline.

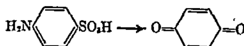


$$2\,HNO_3 + H_2NC_6H_4SO_2OH \longrightarrow H_2NC_6H_3(NO_2)_2 + H_2O + H_2SO_4$$

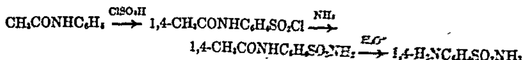
On diazotization, sulfanilic acid is converted into diazobenzenesulfonic acid.



A mixture of dichromate and sulfuric acid oxidizes sulfanilic acid to *p*-benzoquinone.



Sulfanilamide, 1,4-$H_2NC_6H_4SO_2NH_2$. This is prepared from acetanilide.



$$CH_3CONHC_6H_5 \xrightarrow{ClSO_3H} 1,4\text{-}CH_3CONHC_6H_4SO_2Cl \xrightarrow{NH_3} 1,4\text{-}CH_3CONHC_6H_4SO_2NH_2 \xrightarrow{H_2O} 1,4\text{-}H_2NC_6H_4SO_2NH_2$$

Acetanilide is sulfonated with chlorosulfonic acid to *p*-acetamidobenzenesulfonyl chloride, and this gives *p*-acetamidobenzenesulfonamide (acetsulfanilamide) with ammonia. The latter on hydrolysis gives sulfanilamide, because, of the two amide groups, the one from a carboxylic acid is hydrolyzed much faster than one [illegible] sulfonic acid. Sulfanilamide when taken internally checks the growth of [illegible]

genic microorganisms in the body and thus aids in the control of many diseases. It is the simplest of the sulfa drugs. There is danger in its use because it can diminish the number of white corpuscles in the blood and can cause damage to the kidneys.

There are a large number of sulfa drugs known. They have the general structure $H_2NC_6H_4SO_2NH$—Y, where Y usually is the radical of some ring system (pyridine, quinoline, diazine, thiazole, etc.; Chap. 45). Sulfa drugs had quite a vogue in the decade following 1935, but now are largely supplanted by natural antibiotics from molds and bacteria, for example, penicillin, streptomycin, aureomycin, chloromycetin, and terramycin.

Identification of Aromatic Amines. Aromatic amines in general are slightly soluble in water, readily soluble in aqueous hydrochloric acid. Addition of a base to the acid solution throws down the amine. Aqueous solutions of the amines give precipitates on the addition of bromine water, but the test is not characteristic since phenols act similarly.

The class to which an amine belongs may be ascertained by the tests that are applicable to aliphatic amines, except for the reaction with nitrous acid. A primary aliphatic amine yields nitrogen with this reagent, while a primary aromatic amine gives a soluble diazonium salt and this, in turn, evolves nitrogen when the solution is heated. A more sensitive test is addition of a few drops of the diazonium solution to a solution of a phenol in dilute aqueous base. One of the best for the purpose is β-naphthol. A brightly colored precipitate indicates a diazonium salt, and thus a primary aromatic amine originally. The reaction with benzene (or toluene) sulfonyl chloride in the presence of aqueous sodium hydroxide (Hinsberg's test) is one of the best methods of distinguishing primary, secondary, and tertiary aromatic amines (p. 458).

The identification of an amine is made complete by converting it to a solid derivative and identifying this by the melting point. Solid derivatives of primary and secondary amines may be obtained by reaction with acyl halides or anhydrides (p. 356) or with isocyanates (p. 396).

PROBLEMS

1. Show the steps (reagents and conditions) for a practical preparation of the following from benzene and any aliphatic compound but without using the reactions of diazonium compounds of Chapter 32.

a) *o*-nitroacetanilide
b) *m*-nitroacetanilide
c) *p*-nitroacetanilide
d) 2,4-dinitroacetanilide
e) 2-bromo-4-nitroacetanilide
f) 2-acetamido-5-nitrobenzenesulfonyl chloride
g) *m*-aminoformanilide
h) benzenesulfon-*p*-nitroanilide
i) *p*-aminoacetanilide
j) 3-nitro-4-acetamidobenzenesulfonyl chloride
k) 2-acetamido-5-nitrobenzenesulfonamide

l) 3-bromo-4-acetamidobenzenesulfonamide
m) 2-chloro-4-bromoacetanilide
n) *o*-diaminobenzene
o) 2-chloro-4-nitropropionanilide
p) 2-bromo-4-nitroaniline
q) 2,5-diaminobenzenesulfonamide
r) 3,4-diaminobenzenesulfonamide
s) *p*-nitro-N,N-dimethaniline
t) benzenesulfon-*o*-nitroanilide
u) *p*-N,N-dimethylaminobenzenesulfonamide
v) *p*-amino-N,N-dimethylbenzenesulfonamide

2. Ditto, but toluene instead of benzene:

a) acet-*p*-toluidide
b) N-benzylacetamide
c) *o*-aminotoluene-*p*-sulfonamide
d) form-*o*-toluidide
e) *p*-aminotoluene-*o*-sulfonic acid
f) *o*-aminobenzoic acid
g) *o*-bromo-*p*-propionamidotoluene
h) *o*-amino-*n*-propylbenzene
i) *o*-chloro-*p*-aminotoluene
j) *p*-aminobenzoic acid
k) *o*-nitro-*p*-aminotoluene
l) *o*-amino-*p*-nitrotoluene
m) *p*-acetamidotoluene-*o*-sulfonamide
n) *m*-bromo-*p*-N-methylaminotoluene
o) *m*-nitro-*p*-acetamidotoluene
p) *m*-chloro-*p*-formamidotoluene
q) *p*-toluenesulfon-*p*-toluidide
r) *p*-toluenesulfon-*o*-toluidide
s) *p*-acetamidotoluene-*m*-sufonyl chloride
t) 2-dimethylamino-5-nitrosotoluene

3. Write the structure of the compound that would be expected to rearrange so as to yield:

a) 2-methylamino-5-nitrosotoluene
b) 2-methylamino-3-nitrotoluene
c) 4-amino-*m*-xylene
d) 2-aminomesitylene
e) 2,5-diaminodiphenylamine
f) 2,2'-dimethyl-4,4'-diaminobiphenyl
g) 3-nitro-4-ethylaminotoluene
h) 2-amino-5-hydroxyphenetole
i) 3-nitroso-4-*n*-propylaminotoluene
j) 2-chloro-4-hydroxyaniline
k) 4-methylamino-5-sulfo-*m*-xylene
l) 3-methoxy-4-hydroxyaniline
m) 2-methyl-4-ethylaniline
n) 2-bromo-3'-methoxy-4,4'-diaminobiphenyl
o) 2-amino-5-hydroxytoluene
p) 2-hydroxy-5-aminotoluene
q) 4-methoxy-4'-aminodiphenylamine
r) 3-sulfo-4-ethylaminotoluene

s) 2-methylamino-5-nitroso-*m*-xylene
t) 2-amino-5-hydroxy-*m*-xylene

4. Describe a convenient chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) *o*-bromoaniline and aniline hydrobromide
b) *o*-chloroacetanilide and N-chloroacetanilide
c) *p*-chloroaniline and *p*-chloro-N-methylaniline
d) *p*-chloroaniline and *p*-chloro-N,N-dimethylaniline
e) *p*-chloro-N-methylaniline and *p*-chloro-N,N-dimethylaniline
f) acetanilide and acet-*p*-toluidide
g) diphenylamine and acet-*p*-toluidide
h) diphenylamine and hydrazobenzene
i) sulfanilamide and acetsulfanilamide
j) sulfanilic acid and ethyl sulfanilate
k) ethylaniline nitrosoamine and *p*-nitroso-N-ethylaniline
l) *p*-ethylaniline and N-ethylaniline
m) *p*-ethyl-N-ethylaniline and N,N-diethylaniline
n) 2,4-diethylaniline and N,N-diethylaniline
o) aniline and cyclohexylamine
p) *p*-toluidine and *p*-methylcyclohexylamine
q) di-*n*-butylamine and N-*n*-butylaniline
r) tri-*n*-butylamine and N,N-di-*n*-butylaniline
s) *p*-toluidine and benzylamine
t) benzenesulfonanilide and benzenesulfon-N-methylanilide

5. Describe a convenient procedure (reagent, conditions, solvent if any, and separation technique) by which the first named component of the following mixture can be recovered, free of the other, and essentially quantitatively.

a) aniline and *p*-cymene
b) durene and N,N-dimethylaniline
c) iodobenzene and aniline
d) acetanilide and *m*-nitroaniline
e) *p*-toluidine and *n*-butyric acid
f) *o*-chloroaniline and nitrobenzene
g) N,N-diethylaniline and *p*-ethyl-N-ethylaniline
h) N,N-dimethylaniline and 2,4-dimethylaniline
i) [illegible] and *m*-dinitrobenzene
j)
k)
l) *p*-chloroaniline and sulfamic acid
m) acetsulfanilamide and sulfanilamide
n) *p*-toluidine and acet-*p*-toluidide
o) *o*-toluidine and silica gel
p)
q)
r)
s)
t)

6. Compound *A*, C_7H_9N, only slightly soluble in water or in dilute aqueous base, dissolves in dilute aqueous hydrochloric acid. *A* and acetic anhydride give *B*, $C_9H_{11}ON$, *insoluble* in water or in dilute acids or bases. When *B* is heated with neutral, buffered aqueous permanganate, it slowly dissolves. Addition of hydrochloric acid to the resulting solution

precipitates a solid, *C*, $C_8H_9O_3N$. When this is mononitrated with the proper amount of nitrating mixture, only one derivative can be isolated. What deductions can be drawn from these statements? Show how they lead to a structure for *A*.

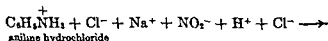
7. Compound *A*, $C_8H_9O_2N$ is insoluble in water and in dilute aqueous acid or base. It slowly dissolves on the addition of stannous chloride in hydrochloric acid. Steam distillation from an alkaline solution gives *B*, $C_8H_{11}N$, insoluble in water and aqueous base, slowly soluble in aqueous base plus benzenesulfonyl chloride. Addition of hydrochloric acid precipitates *C*, $C_{14}H_{15}O_2NS$. Oxidation of *C* with neutral permanganate gives *D*, $C_{14}H_{13}O_4NS$. Nitration of *D* with some excess of nitrating mixture gives only one mononitro compound, *E*, $C_{14}H_{12}O_6N_2S$. What deductions can be drawn from these statements? Show how they lead to a structure for *A*.

CHAPTER 32

Diazo Compounds

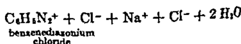
The diazo compounds are remarkable not only from the standpoint of chemical reactivity but also from that of structure. They are important in the manufacture of a valuable group of dyes, the azo dyes. They were named by Greiss, who discovered them in 1860, to indicate the presence of two nitrogen atoms in the molecule (Fr. *azote*, nitrogen).

Diazotization. When an aryl amine in the presence of a strong acid reacts with nitrous acid or with its anhydride, the amine is said to be diazotized, for the product is a diazonium salt. Nitrous acid is generated by the reaction between a nitrite and an acid



$$C_6H_5\overset{+}{N}H_3 + Cl^- + Na^+ + NO_2^- + H^+ + Cl^- \longrightarrow$$

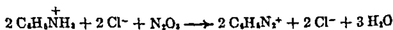
aniline hydrochloride



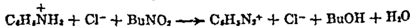
$$C_6H_5N_2^+ + Cl^- + Na^+ + Cl^- + 2\,H_2O$$

benzenediazonium chloride

The product can be obtained as a solid by carrying out the reaction in glacial acetic acid with nitrous anhydride or butyl nitrite.



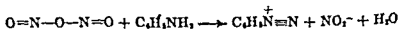
$$2\,C_6H_5\overset{+}{N}H_3 + 2\,Cl^- + N_2O_3 \longrightarrow 2\,C_6H_5N_2^+ + 2\,Cl^- + 3\,H_2O$$



$$C_6H_5\overset{+}{N}H_3 + Cl^- + BuNO_2 \longrightarrow C_6H_5N_2^+ + Cl^- + BuOH + H_2O$$

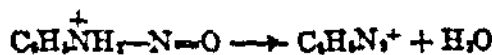
On the addition of ethyl ether to the resulting solution the diazonium chloride separates, owing to its saltlike structure.

The diazotization reaction is first order in aniline and second order in nitrous acid. A mechanism consistent with this could involve a reaction of nitrous anhydride with aniline.



$$O{=}N{-}O{-}N{=}O + C_6H_5NH_2 \longrightarrow C_6H_5\overset{+}{N}{\equiv}N + NO_2^- + H_2O$$

Phenylnitrosammonium ion, $C_6H_5\overset{+}{N}H_2{-}N{=}O$, is believed to be a transient intermediate.

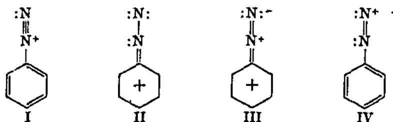


$$C_6H_5\overset{+}{N}H_2{-}N{=}O \longrightarrow C_6H_5N_2^+ + H_2O$$

Properties of Diazonium Salts. Benzenediazonium chloride is a colorless solid, very soluble in water. The diazonium chlorides from most of the simpler amines also are quite soluble in water, less soluble in alcohol, and only slightly soluble in ether. Benzenediazonium chloride is unstable when dry and may explode when heated. Nitrates and perchlorates are still less stable. Nitrates when dry may explode on rubbing, and perchlorates even when wet. The explosibility of salts from higher aryl amines usually decreases with increase in molecular weight. Some salts are quite stable. Sulfates are more stable than chlorides, and arylsulfonates still more stable. For industrial purposes the stable salts are double salts of sodium naphthalenesulfonate and diazonium naphthalenesulfonate.

The saltlike nature of benzenediazonium chloride is shown not only by its low solubility in ether but also by the abnormal depression of the freezing point of its aqueous solution and by the high conductivity. The salt cannot be recovered from the aqueous solution by evaporation because it decomposes in contact with water, slowly in cold water, rapidly in hot water (see Reactions). The solution of benzenediazonium chloride in water is neutral. This shows that the base from which the salt is derived is a strong base.

Structure of Diazonium Salts. These are composed of a positive diazonium ion and a negative anion. The stability of the diazonium ion can be ascribed to resonance involving the benzene ring, because with few exceptions, diazonium compounds are known only in those cases where the diazonium group is attached to an aromatic nucleus. The more stable resonance forms are shown as I to IV, where I and IV each represent two Kekulé forms and II and III each represent three resonance forms with the *ortho-* and *para-*carbon atoms carrying the positive charge (p. 442).



Other forms also can be written but they are much less stable. Thus I to IV represent ten resonance forms. The multiplicity of resonance forms contributes to the stability of the molecule. The resistance to nitration and the *meta*-orientation of the diazonium group are consistent with a positively charged nucleus (p. 441).

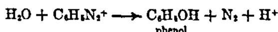
Reactions of Diazonium Salts. There are three general types of reactions: (1) replacement, in which the N_2Cl group is replaced by some other univalent group, for example, chloro, hydroxyl, or cyano; (2) coupling, in which the ArN_2 group becomes attached to a carbon atom, usually one in an aromatic ring, or to a nitrogen atom of an amino group; and (3) reduction. In the replacement reactions two atoms of nitrogen are lost as molecular nitrogen, in

coupling they are retained as an azo linkage (p. 488), and in reduction also they are retained.

Usually the reactions are carried out in aqueous solution. Only rarely is it necessary to work under anhydrous conditions or with the dry salts.

Replacement. Because of the large number of radicals that can replace the diazonium group, these compounds are important in synthesis and play a role in the aromatic series comparable to that played by alkyl halides in the aliphatic. On this account aryl primary amines and also the nitro compounds are valuable in synthesis. The more common of the replacement reactions are described below. The reactions of benzenediazonium chloride are characteristic of other similar compounds.

1. *Hydroxyl.* Slowly in the cold, more rapidly when heated to 60°, the diazonium salt reacts with water; nitrogen is evolved and phenol is formed.



$$H_2O + C_6H_5N_2^+ \longrightarrow \underset{\text{phenol}}{C_6H_5OH} + N_2 + H^+$$

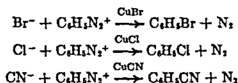
The final result is the same as with a primary aliphatic amine, *viz.*, replacement of the amino group by hydroxyl. This reaction usually is a side reaction when other replacements are being carried out in aqueous solution.

2. *Iodo.* Iodide ion reacts when added to the acidic solution; nitrogen is evolved and an aryl iodide is formed.



$$I^- + C_6H_5N_2^+ \longrightarrow C_6H_5I + N_2$$

3. *Bromo, chloro, cyano, and fluoro; the Sandmeyer reaction.* There is some replacement by bromo, chloro, and fluoro in concentrated aqueous acids but the yields usually are low. In the presence of cuprous bromide, cuprous chloride, and cuprous cyanide, the diazonium group is replaced by bromo, chloro, and cyano, respectively (the Sandmeyer method). The diazotizations are carried out with hydrobromic, hydrochloric, and sulfuric acid, respectively.



$$Br^- + C_6H_5N_2^+ \xrightarrow{CuBr} C_6H_5Br + N_2$$
$$Cl^- + C_6H_5N_2^+ \xrightarrow{CuCl} C_6H_5Cl + N_2$$
$$CN^- + C_6H_5N_2^+ \xrightarrow{CuCN} C_6H_5CN + N_2$$

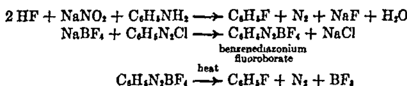
The reactions actually are more complicated because an addition compound is first formed, and this decomposes to the cuprous salt and the desired product. A modification is the use of copper powder in place of the cuprous salt (Gattermann method). A side reaction, which sometimes can be made the main reaction, is biphenyl coupling, as with copper powder and benzenediazonium sulfate.



$$Cu + 2\,C_6H_5N_2^+ \longrightarrow \underset{\text{biphenyl}}{C_6H_5{-}C_6H_5} + 2\,N_2 + Cu^{++}$$

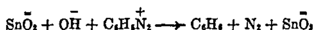
The fluoro group can be introduced by dissolving the amine in cold liquid hydrogen fluoride, adding solid sodium nitrite, and allowing the liquid to

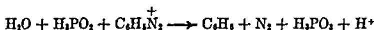
evaporate. A safer and quite convenient method involves precipitation of a diazonium fluoroborate by the addition of sodium fluoroborate to an aqueous solution, and heating the dry salt.



4. *Hydrogen.* A number of reducing agents can be used, *e.g.*, alcohols, alkaline sodium stannite, or hypophosphorous acid.

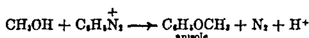






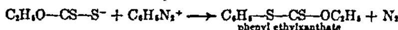
Excellent results have been obtained by heating dry stable diazonium salts, for example those of naphthalene-1,5-disulfonic, in a solvent (alcohols, among others) with zinc dust or copper powder.

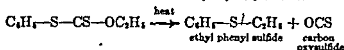
5. *Alkoxy.* This group competes with hydrogen when alcohol is used. The operation often is done with the dry salt.

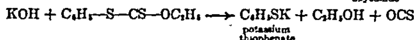


Benzenediazonium chloride yields mainly ether (70%) with methanol, and this decreases as the molecular weight of the alcohol is made larger. Alkyl groups in the diazonium compound favor ether formation; negative groups such as nitro and sulfo favor the hydrocarbon. Higher temperature favors ether.

6. *Thiol,* —SH, *and* Sul*fide,* —SR. One of the most convenient methods involves forming a phenyl alkyl xanthate by reaction with potassium alkyl xanthate (p. 342) and decomposing this by heating alone, to give phenyl alkyl sulfide or hydrolyzing the xanthate to give thiophenol.



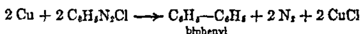




7. *Nitro.* This replacement is accomplished by adding finely divided cuprous oxide to a solution of a diazonium nitrate.



8. *Aryl.* The introduction of this group is called biphenyl coupling, and is a usual side reaction in the Sandmeyer or Gattermann reaction. The diazonium sulfate gives a better yield than the chloride.



$$2\,Cu + 2\,C_6H_5N_2Cl \longrightarrow \underset{\text{biphenyl}}{C_6H_5{-}C_6H_5} + 2\,N_2 + 2\,CuCl$$

A dry diazonium chloride may react with benzene in the presence of anhydrous aluminum chloride.



$$C_6H_6 + C_6H_5N_2Cl \longrightarrow C_6H_5{-}C_6H_5 + N_2 + HCl$$

A generally useful method is the reaction of a diazohydrate with an aromatic liquid by adding aqueous alkali to a suspension of a diazonium salt in the liquid (Gomberg reaction).



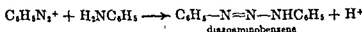
$$C_6H_5N_2OH + C_6H_5Y \longrightarrow p\text{-}C_6H_5{-}C_6H_4{-}Y + N_2 + H_2O$$

This reaction proceeds through a free-radical mechanism and does not follow the usual rules of substitution, for a *para*-compound is formed with C_6H_5Y. Here Y represents any radical, even a *meta*-directing radical such as NO_2 or $COOC_2H_5$.

Coupling. Diazonium salts couple with amines and phenols in weakly acidic, neutral, or basic solutions. The *para*-position is taken preferably, and when this is blocked, the *ortho*-position. Coupling is retarded in strongly acidic solutions. Kinetic studies show that it is the diazonium ion that reacts. The effect of acid is to decrease the reactivity of the amine or phenol, presumably by salt formation. An ammonium ion group, by placing a positive charge on the nitrogen atom, acts to pull electrons out of the ring, and thus diminish its tendency not only to react with electrophilic substituting agents like nitric acid but also to couple with a positive diazonium ion. Phenols also form salts with acids, but higher concentrations are necessary. More than one azo group may enter but not so easily. In the case of phenols, addition of alkali is an aid because the negative ion of phenol, $C_6H_5O^-$, is more reactive than phenol It has been possible to put three azo linkages on one phenol ring this way.

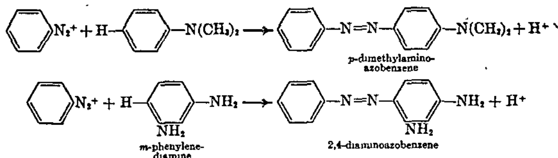
The products with amines are diazoamino or aminoazo compounds; with phenols, hydroxyazo compounds. The aminoazo and hydroxyazo compounds are highly colored and dye silk, wool, skin, hair, and feathers. They constitute a vast number of products, among them many fast and valuable dyes.

1. *Diazoamino coupling.* This is the product with a primary or secondary amine unless an extremely active position is present on the benzene ring.



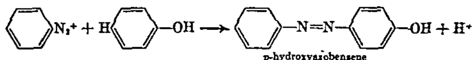
$$C_6H_5N_2^+ + H_2NC_6H_5 \longrightarrow \underset{\text{diazoaminobenzene}}{C_6H_5{-}N{=}N{-}NHC_6H_5} + H^+$$

2. *Aminoazo coupling.* Coupling takes place directly on the benzene ring with a tertiary amine, or with a primary or secondary amine when there is a very reactive position, as in *m*-toluidine or 1,3-diaminobenzene (*m*-phenylenediamine).

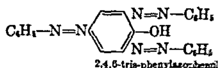


Even with a simple amine it is possible to obtain an aminoazo product, by rearrangement (see Diazoaminobenzene).

3. *Hydroxyazo coupling.* Benzenediazonium chloride and phenol give *p*-hydroxyazobenzene.

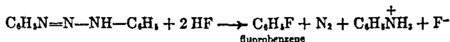


A second azo group can be introduced with an excess of diazonium salt and addition of excess base. A third can be introduced only with difficulty, and in strongly alkaline solution, to give 2,4,6-tris-phenylazophenol.

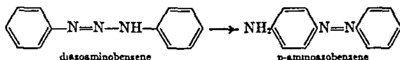


Reduction to Phenylhydrazine. Benzenediazonium chloride can be reduced without elimination of nitrogen. This can be accomplished with stannous chloride under acid conditions, yielding a salt of phenylhydrazine

Diazoaminobenzene is a golden yellow solid, essentially insoluble in water. It is only a very weak base and also has weak acid properties. In alcoholic solution it reacts with silver ion, forming a mono silver salt. It reacts with concentrated aqueous hydrohalic acids, with scission of the bond between NH and N_2 and formation of an aryl halide. This reaction is sometimes used for preparing fluorides.



A molecular rearrangement takes place under weakly acid conditions, preferably on heating to 50° with aniline hydrochloride in aniline (to act as solvent).

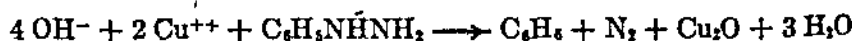


This is another example of migration of a negative radical attached to a nitrogen atom (p 475). The final result of the reaction of diazotized aniline with aniline is the same as if initial coupling took place directly on the ring.

Phenylhydrazine, $C_6H_5NHNH_2$. This is obtained in the form of a salt by acid reduction of benzenediazonium chloride, p. 489. Addition of a strong base liberates the organic base. Phenylhydrazine melts at 19.6° and boils at 241 to 242° with slight decomposition. When obtained by distilling at low pressures (120° at 12 mm.), it is colorless but quickly darkens on exposure to air, due to oxidation. It is monobasic, somewhat stronger than aniline ($K_b = 1.6 \times 10^{-9}$) and yields crystalline salts with acids. The hydrochloride is the common salt and can be used when the free base is wanted, usually by adding sodium acetate. Phenylhydrazine is converted into aniline and ammonia by reducing agents that furnish hydrogen, as for example, zinc and sulfuric acid.



With oxidizing agents different products are obtained. Mercuric oxide, a mild oxidizing agent, converts the sulfate to benzenediazonium sulfate; solutions of ferric chloride, copper sulfate, potassium chromate, etc., when heated, convert phenylhydrazine to benzene. Silver ion and Fehling's solution are reduced in the cold by phenylhydrazine.

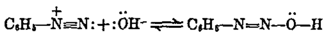


The most important reaction of phenylhydrazine is the formation of phenylhydrazones with aldehydes and ketones (p. 271) and of osazones with the sugars (p. 614). It is significant that Emil Fischer, who discovered phenylhydrazine in 1875, later used it with marked success in his classical work on the structure of sugars.

2,4-Dinitrophenylhydrazine, 2,4-$H_2NNHC_6H_3(NO_2)_2$. Of the large number of substituted phenylhydrazines available for making derivatives of aldehydes and ketones, this is the one most used because all of the derivatives are solids. It is a solid, m p. 194°, and is prepared by the action of hydrazine on 2,4-dinitrochlorobenzene, whose chlorine is activated by the two nitro groups (p. 450).

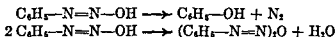
Benzenediazonium Hydroxide, $C_6H_5N_2^+(OH^-)$, and Benzenediazohydroxide, C_6H_5—N═N—OH. The first is the base of which benzenediazonium chloride is a salt, and the second is the acid of which potassium benzenediazotate is a salt. Neither

one of these compounds has been isolated because of instability. Benzenediazonium hydroxide, obtained in solution by the addition of one equivalent of strong base to an aqueous solution of a diazonium salt, passes spontaneously into benzenediazohydroxide (diazobenzenehydrate, diazobenzene).



The reaction is reversible; on the addition of a strong acid benzenediazohydroxide is converted to a diazonium salt.

Benzenediazohydroxide in solution decomposes in a variety of ways, one to yield phenol and nitrogen, another to yield benzenediazoanhydride, an explosive compound.



On the addition of excess base, the hydrate is converted into a salt, for example, potassium benzenediazotate.

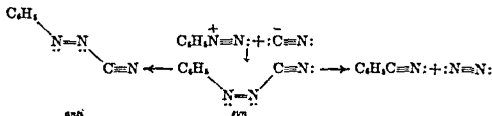


This is a fairly stable compound. Many solid metallic diazotates have been isolated. These are reactive and readily couple with amines and phenols, forming aminoazo and hydroxyazo compounds.

Heating an aqueous solution of potassium benzenediazotate (the normal form) with excess of base causes isomerization to a more stable form, called potassium benzeneisodiazotate. This and similar isodiazotates are much less reactive than the normal forms. The generally accepted explanation of the difference between normal and isodiazotates is stereochemical, similar to *cis,trans*-isomerism of olefinic compounds. In this case they are called *syn*- and *anti*-forms. The normal isomers are believed to have the *syn*; and the isodiazotates the *anti*-configuration.

Mechanisms. The replacement of the diazonium group by various radicals is a nucleophilic attack because the reacting substances are either negative ions or neutral molecules with unshared electron pairs. The reactant attaches itself to the carbon atom holding the diazonium group, which leaves the molecule as a neutral nitrogen molecule. The reaction probably is similar to a displacement reaction of an alkyl halide (p. 113), the bond between carbon and nitrogen breaking as the new bond to carbon is being formed. It should be emphasized that the carbon-to-nitrogen bond in a diazonium compound is cleaved much more easily than an ordinary carbon-to-nitrogen bond (diazomethane is also very reactive).

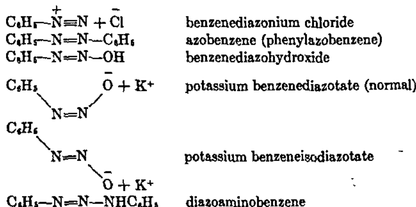
There are intermediate steps, and these are known in some cases; for example cyanide ion reacts to form benzenediazocyanide, which exists in *syn*- and *anti*-forms. The *syn*-form decomposes easily to phenyl cyanide on the addition of copper powder, and couples with phenols. The *anti*-isomer, formed on standing, is less reactive, both with copper powder and with phenols.



In the *syn*-form the carbon atom of the cyanide group can swing over to the benzene carbon atom to form the new bond while the nitrogen atom lets go.

Diazocyanides differ from most azo compounds where the —N=N— group joins two carbon atoms, for in general these are relatively stable compounds.

Nomenclature. The name diazo was given to the first discovered compounds, now called the diazonium salts. Azo compounds were originally named to show the two radicals that are joined by the two nitrogen atoms, and such names are still sometimes used, for example, benzeneazo-β-naphthol.



PROBLEMS

1. Show the steps (reagents and conditions) for a practical preparation of the following from any aliphatic compound and benzene, through the diazo reaction:

a) *o*-chloronitrobenzene
b) *m*-fluoronitrobenzene
c) *p*-iodonitrobenzene
d) *o*-nitrobenzonitrile
e) *m*-nitrobenzonitrile
f) *p*-nitrobenzonitrile
g) *o*-fluoroacetanilide
h) *m*-iodoacetanilide
i) *p*-fluoroacetanilide
j) *o*-iodophenol
k) *m*-bromophenol
l) *p*-fluorophenol
m) *o*-chloro-*p*-fluoroacetanilide
n) *m*-bromo-*p*-iodoacetanilide
o) *o*-fluorophenylhydrazine
p) *o*-bromo-*p*-cyanoacetanilide
q) 2-cyano-5-nitrobenzenesulfonic acid
r) *o*-fluorobenzenesulfonic acid
s) 2-acetamido-5-iodobenzenesulfonic acid
t) *o*-bromo-*p*-nitrophenol

2. Ditto, but from toluene:

a) *o*-bromotoluene
b) *m-bromotoluene*
c) *p*-bromotoluene
d) *o*-iodotoluene
e) *m*-iodotoluene
f) *p*-iodotoluene
g) *o*-cyanotoluene
h) *m*-cyanotoluene
i) *p*-cyanotoluene
j) *o*-fluorotoluene
k) *m*-fluorotoluene
l) *p-fluorotoluene*
m) *o*-iodo-*p*-nitrotoluene
n) *o*-cyano-*p*-nitrotoluene
o) *o*-bromo-*p*-aminotoluene
p) *o*-fluoro-*p*-acetamidotoluene
q) *o*-acetamido-*p*-iodotoluene
r) *o*-amino-*p*-fluorotoluene
s) *o*-nitro-*p*-bromotoluene
t) *o*-nitro-*p*-cyanotoluene

3. Ditto, but from *p*-nitrotoluene.

a) *m*-nitro-*p*-bromotoluene
b) *m*-acetamido-*p*-fluorotoluene
c) *p*-cyanotoluene-*m*-sulfonic acid
d) 3,4-dichlorotoluene
e) *m*-amino-*p*-chlorotoluene
f) *m*-bromo-*p*-cyanotoluene
g) *o*-chlorobenzylamine
h) *p*-bromotoluene-*m*-sulfonchloride
i) *m*-iodo-*p*-cyanotoluene
j) *m*-cyano-*p*-iodotoluene
k) *p*-iodotoluene-*m*-sulfonamide
l) *m*-bromo-*p*-fluorotoluene

4. Ditto, but from nitrobenzene and/or *o*-nitrotoluene and/or *p*-nitrotoluene.

a) *p*-diethylaminoazobenzene
b) 2-dimethylamino-5-nitroazobenzene
c) *p*-methyl-*p*′-dimethylaminoazobenzene
d) 2-amino-5,4′-dimethylazobenzene
e) 3-nitro-4-hydroxy-4′-methylazobenzene
f) 2-hydroxy-5,2′-dimethylazobenzene
g) 3-fluoro-4-hydroxy-4′-methylazobenzene
h) 3-fluoro-4-dimethylamino-2′-methylazobenzene
i) 2-fluoro-4-dimethylamino-4′-methylazobenzene
j) 2-diethylamino-5,4′-dimethylazobenzene
k) 2-iodo-4-hydroxy-5,2′-dimethylazobenzene
l) 2-bromo-4-dimethylamino-3′-methylazobenzene
m) 3-cyano-4-hydroxy-4′-methylazobenzene
n) 2,4-diamino-3′-sulfo-4′-methylazobenzene
o) 4-hydroxy-2,3′-dimethylazobenzene
p) 3,4′-bis-dimethylaminoazobenzene
q) 2,5,4′-tris-dimethylaminoazobenzene
r) 2-hydroxy-4′-sulfo-4-methylazobenzene
s) 2-bromo-4-acetamido-4′-hydroxy-3′-methylazobenzene
t) 2-sulfo-4′-amino-4,2′-dimethylazobenzene
u) 2-diethylamino-3′-sulfo-5,4′-dimethylazobenzene
v) 2-dimethylamino-3-nitro-3′-bromo-5,4′-dimethylazobenzene

CHAPTER 33

Phenols

There are two classes of aromatic hydroxyl derivatives, *viz.*, the aromatic alcohols (Chap. 34), compounds in which the hydroxyl group is attached to a side chain, and the phenols, compounds in which it is attached directly to the benzene nucleus. The name of the simplest member, phenol, C_6H_5OH, denotes phenyl and hydroxyl groups.

Phenols are produced in the pyrogenic decomposition of wood and coal. Coal tar for many decades was the main source of phenol and the cresols. They are constituents of the "light oil" and "heavy oil" fractions. A method of removal that has been standard practice for many decades is agitation of a narrower cut from refractionation, about 160 to 250°, with aqueous base. After distillation with steam to remove small amounts of nonacidic compounds, addition of excess acid liberates the phenols. Another method is agitation with sulfuric acid. The phenols are removed by steam distillation, after water has been added (p. 457).

Industrial production of synthetic phenol was carried out in the United States during World War I and has been expanded markedly since that time. The first method was based on the fusion of benzenesulfonic acid with alkali (p. 458); later the hydrolysis of chlorobenzene was perfected (p. 452). The ideal method would be partial oxidation of benzene to phenol.

$$O_2 + 2\,C_6H_6 \longrightarrow 2\,C_6H_5OH$$

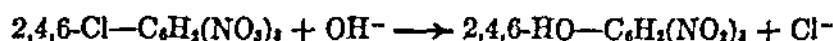
This is difficult to accomplish because phenol is more easily oxidized than benzene. The requirements are, a fairly high temperature, a short reaction time, and some other substance to promote the reaction, usually a solid catalyst, sometimes a volatile catalytic substance. Many investigations have been and are being made along these lines.



Preparation of Phenols. In ordinary laboratory work the most convenient method is decomposition of diazonium salts when heated in aqueous solution (p. 486). The method from the sulfonic acid fusion is less convenient and may lead to other changes, such as removal of a halogen atom, if one is present, oxidation to a dihydric phenol, or intramolecular oxidation and reduction, if a nitro group or other oxidizing group is present. A com-

plication in the diazonium salt reaction is the formation of an azo compound by coupling between the diazonium salt and the phenol.

Some nitrophenols can be obtained from nitrochloro or nitrobromo compounds, owing to the activating influence of a nitro group, especially when it is in the *ortho*-position (p. 450). Picric acid (2,4,6-trinitrophenol) is obtained from picryl chloride by the action of a base in aqueous alcohol.



$$2,4,6\text{-Cl—}C_6H_2(NO_2)_3 + OH^- \longrightarrow 2,4,6\text{-HO—}C_6H_2(NO_2)_3 + Cl^-$$

Properties of Phenols. They are solids or liquids of moderately high boiling point, good solubility in ordinary organic solvents, and slight solubility in water. The water solubility rises with increase in the number of hydroxyl groups. The phenyl radical enhances the acidic property of water It will be recalled that it diminishes the basic property of ammonia, for aniline is a weaker base than ammonia Phenol is a much stronger acid than water.

Reactions of Phenols. Of the following reactions the first four are those of the hydroxyl group, the last five are those of the benzene ring, and the fifth applies to both. It will be noted that: (1) phenols are stronger acids than alcohols (Tables 38, p. 139, and 88); (2) esterification is not as easy as

TABLE 88 | **Constants of Some Phenols**

NAME	FORMULA	M.P. °C	B P. °C	SOLY. IN H_2O 25° G./100 G	K_a
Phenol	C_6H_5OH	40 9	182 2	9.3	1.1×10^{-10}
o-Cresol	1,2-$CH_3C_6H_4OH$	30.95	191.0	2.5	$6\,3 \times 10^{-11}$
m-Cresol	1,3-$CH_3C_6H_4OH$	10 8	201	2 6	9.8×10^{-11}
p-Cresol	1,4-$CH_3C_6H_4OH$	34.78	201 9	2.3	6.7×10^{-11}
Carvacrol	1,2,4-$CH_3C_6H_3(OH)C_3H_7$-*i*	0.5	238		4.5×10^{-11}
Thymol	1,3,4-$CH_3C_6H_3(OH)C_3H_7$-*i*	51.5	232.8	0 098	$3\,2 \times 10^{-11}$
o-Fluorophenol	1,2-HOC_6H_4F	16.1	151–152		1.5×10^{-9}
m-Fluorophenol	1,3-HOC_6H_4F	13 8	177.8		5.2×10^{-10}
p-Fluorophenol	1,4-HOC_6H_4F	48	185.5		1.1×10^{-10}
o-Chlorophenol	1,2-HOC_6H_4Cl	8.8	173	2.8	7.7×10^{-9}
m-Chlorophenol	1,3-HOC_6H_4Cl	32.8	214	2 6	$1\,6 \times 10^{-9}$
p-Chlorophenol	1,4-HOC_6H_4Cl	42.9	219 7	2 7	$6\,3 \times 10^{-10}$
o-Bromophenol	1,2-HOC_6H_4Br		194		$4\,1 \times 10^{-9}$
m-Bromophenol	1,3-HOC_6H_4Br	33	236		1.4×10^{-9}
p-Bromophenol	1,4-HOC_6H_4Br	64	235–236		$5\,6 \times 10^{-10}$
o-Nitrophenol	1,2-$HOC_6H_4NO_2$	45.13	217.2	0 2	6.0×10^{-8}
m-Nitrophenol	1,3-$HOC_6H_4NO_2$	96	194^{70}	1 35	$0\,5 \times 10^{-8}$
p-Nitrophenol	1,4-$HOC_6H_4NO_2$	114		1.69	6.9×10^{-8}
Dinitrophenol	1,2,4-$HOC_6H_3(NO_2)_2$	113		0.56	1×10^{-4}
Picric acid	1,2,4,6-$HOC_6H_2(NO_2)_3$	122	expl 300°	1.38	2.3×10^{-1}

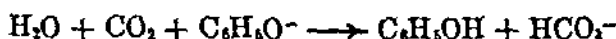
with alcohols; (3) the benzene ring is so activated by the hydroxyl group (p. 442) that not only substitution but also condensation and oxidation reactions take place readily at *ortho-* and *para*-positions.

1. *Acidic and basic properties.* Salts are formed in aqueous solution by the action of strong bases. Sodium hydroxide gives sodium phenoxide (phenate) with phenol.



$$OH^- + C_6H_5OH \longrightarrow C_6H_5O^- + H_2O$$

There is some reversal, because phenols, although much stronger acids than water and alcohols, still are weak acids (Table 88). Sodium and potassium salts of the simple phenols are soluble in water. On exposure to air the salts are decomposed, owing to the action of carbonic acid ($K_1 = 3 \times 10^{-7}$; $K_2 = 6 \times 10^{-11}$).



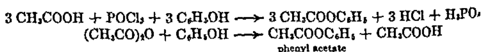
$$H_2O + CO_2 + C_6H_5O^- \longrightarrow C_6H_5OH + HCO_3^-$$

Nitro groups in *ortho-* and *para-*positions enhance acidic properties; thus *o-* and *p*-nitrophenols dissolve in aqueous sodium carbonate, and 2,4,6-trinitrophenol is a strong acid. It is called picric acid (p. 508).

Phenols show the properties of weak bases under anhydrous conditions, by coordination with protons. As an example, *p*-cresol forms two tolyhydronium sulfates with anhydrous sulfuric acid, *viz.*, $2\ CH_3{-}C_6H_4{-}OH \cdot H_2SO_4$, m.p. 11°, and $CH_3{-}C_6H_4{-}OH \cdot 2\ H_2SO_4$, m.p. 93°. These are decomposed on the addition of water.

2. *Ether formation.* Alkyl aryl ethers are produced by the action of alkylating agents on salts of phenols, by the reaction of alcohols with phenols over hot dehydration catalysts (for example, thorium oxide at 420°) or of alcohols with diazonium salts (p. 487).

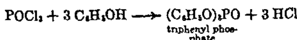
3. *Ester formation.* Direct esterification with the acid alone usually is not satisfactory; instead, the acid plus an inorganic acid halide, for example, phosphorus oxychloride or thionyl chloride, or the organic acyl halide or anhydride, may be heated with the phenol.



$$3\ CH_3COOH + POCl_3 + 3\ C_6H_5OH \longrightarrow 3\ CH_3COOC_6H_5 + 3\ HCl + H_3PO_4$$

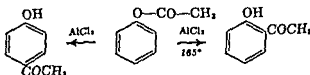
$$(CH_3CO)_2O + C_6H_5OH \longrightarrow \underset{\text{phenyl acetate}}{CH_3COOC_6H_5} + CH_3COOH$$

Phosphorus oxychloride alone reacts slowly with phenols at refluxing temperature. The products are phosphates, industrial products used extensively as plasticizers in polymeric materials (Lucite, polystyrene, etc.).



$$POCl_3 + 3\ C_6H_5OH \longrightarrow \underset{\text{triphenyl phosphate}}{(C_6H_5O)_3PO} + 3\ HCl$$

Phenyl acetate undergoes rearrangement to 4-hydroxyacetophenone on standing with aluminum chloride in nitrobenzene, and to 2-hydroxyacetophenone, when heated to 165° with aluminum chloride.



Other esters react similarly. Migration of the acyl group, especially if a lower one, takes place preferentially to the *para*-position at temperatures of 60° and lower, provided this position is open.

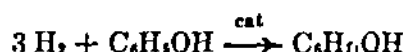
4. *Replacement by halogen.* The hydroxyl group of a phenol, unlike that of an alcohol, is not easily replaced by a halogen atom in a reaction with an inorganic acid halide such as phosphorus oxychloride. Instead, the product is an ester (3, above).

5. *Reduction.* Phenols are reduced to hydrocarbons when the vapor is passed over a hot, finely divided metal (zinc, iron).



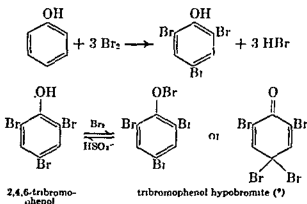
$$Zn + C_6H_5OH \longrightarrow C_6H_6 + ZnO$$

Phenol can be hydrogenated to cyclohexanol. Reaction may proceed at ordinary temperature in the presence of platinum oxide or colloidal platinum, at 100° or higher with Raney nickel, or, as in industry at 180 to 270° with a less active nickel catalyst, prepared by the reduction of nickel oxide with hydrogen.



$$3\,H_2 + C_6H_5OH \xrightarrow{cat} C_6H_{11}OH$$

6. *Halogenation.* In aqueous solution the reaction of a phenol with aqueous bromine or chlorine is very rapid. A solid separates and this may have a variable composition because under these conditions the rates of formation of di- and trisubstituted products also are fast. With three moles of halogen the trisubstituted product is formed from phenol and from any derivative in which the *para*- and the two *ortho*-positions are open. Sometimes a group present is removed; for example, a carboxyl group in the *ortho*-position is replaced by halogen (see Salicylic Acid, p. 535). With an excess of bromine (or chlorine) a yellow tetrahalo derivative is formed, which is reduced by bisulfite ion or other suitable reducing agent back to the trihalo derivative. The structure of the tetrabromo compound is believed to be that of a hypobromite but there is some uncertainty about this



2,4,6-tribromophenol tribromophenol hypobromite (?)

In glacial acetic acid phenol can be smoothly halogenated to a mono or dihalophenol, by use of the proper amount of halogen.

7. *Sulfonation.* Phenol is easily sulfonated to a mixture of *o*- and *p*-phenolsulfonic acids at 15 to 20°, and to the *para*-isomer, at 90 to 100°, with the

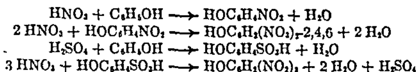
calculated amount of concentrated sulfuric acid, or with a 10 to 50 per cent excess of sulfuric acid monohydrate.



$$H_2SO_4 + C_6H_5OH \longrightarrow HOC_6H_4SO_2OH + H_2O$$

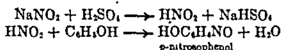
With a large excess of sulfuric acid, a disulfonic acid is obtained.

8. *Nitration and Nitrosation.* Phenol is easily nitrated by dilute nitric acid to a mixture of *o*- and *p*-nitrophenols. Trinitrophenol-2,4,6 (picric acid) results from further nitration but is obtained best by the action of nitric-sulfuric acid on phenolsulfonic acid. The sulfonic acid group is finally replaced by a nitro group. There is less oxidation than when phenol is nitrated directly to trinitrophenol.



$$HNO_3 + C_6H_5OH \longrightarrow HOC_6H_4NO_2 + H_2O$$
$$2\,HNO_3 + HOC_6H_4NO_2 \longrightarrow HOC_6H_2(NO_2)_3\text{-}2,4,6 + 2\,H_2O$$
$$H_2SO_4 + C_6H_5OH \longrightarrow HOC_6H_4SO_3H + H_2O$$
$$3\,HNO_3 + HOC_6H_4SO_3H \longrightarrow HOC_6H_2(NO_2)_3 + 2\,H_2O + H_2SO_4$$

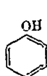
Phenol readily undergoes nitrosation with dilute aqueous acid and an alkali nitrite, yielding a greenish colored solution.



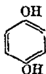
$$NaNO_2 + H_2SO_4 \longrightarrow HNO_2 + NaHSO_4$$
$$HNO_2 + C_6H_5OH \longrightarrow \underset{p\text{-nitrosophenol}}{HOC_6H_4NO} + H_2O$$

The compound is tautomeric with quinone monoxime (p. 544).

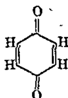
9. *Oxidation.* Phenols are easily oxidized. The darkening of phenols that gradually takes place on exposure to air results from the formation of complicated, highly colored, oxidation products. Intermediate products probably are *o*- and *p*-dihydroxybenzene. These two compounds have actually been obtained from phenol by electrolytic oxidation and by oxidation with peroxysulfuric acid (persulfuric acid). Since these dihydroxy compounds are even more easily oxidized than phenol itself, it is not surprising that the oxidation should in general proceed further and yield other products. Potassium permanganate, for example, causes a complete breakdown of the benzene ring with the formation of *meso*-tartaric acid (p. 408). The steps involved in this oxidation probably proceed through dihydroxybenzene, quinone, and maleic acid. Quinone can be obtained by oxidation of hydroquinone with chromic acid mixture (p. 542).



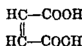
phenol



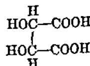
hydroquinone



quinone



maleic acid



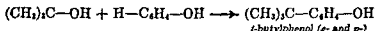
meso-tartaric acid

Homologs of phenol are readily and destructively oxidized by alkaline permanganate solution and by chromic acid mixture However, if the

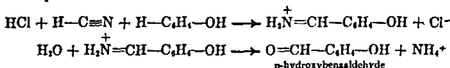
phenol-hydrogen atom is replaced by an alkyl or acyl radical (as in ethers or esters, respectively), then the side-chain alkyl radical is oxidized, and acids are produced having an ether or ester group on the ring (p. 506).

10. *Condensation reactions.* The negative charge that resonance puts on the *ortho-* and *para-*carbon atoms makes phenols nucleophilic reagents. They react with alcohols to produce alkyl phenols. They react with many of the compounds that are reactive with organometallic compounds, for example, carbon dioxide, nitriles, aldehydes, and anhydrides. They react also with carbon tetrachloride and chloroform, compounds of the same oxidation stages as carbonic and formic acids, respectively. They readily couple with diazonium salts. Each reaction can be pictured as a nucleophilic attack of an aromatic carbon atom with its electron pair. It attacks a carbon atom at the positive end of a dipole, except in diazo coupling, when it attacks a nitrogen atom (p. 563).

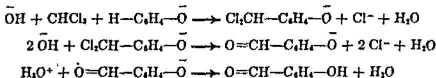
a) With alcohols. Tertiary alcohols are the most reactive When phenol and tertiary butyl alcohol are heated with a suitable catalyst (zinc chloride, aluminum chloride), condensation takes place, preferably at the *para-*position.



b) With hydrogen cyanide. Hydroxy aldehydes are obtained by a reaction with anhydrous hydrogen cyanide and hydrogen chloride in contact with aluminum chloride. The first product, an aldimine salt, is hydrolyzed by dilute aqueous acid.

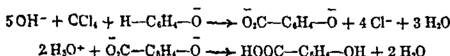


c) With chloroform; the Reimer-Tiemann reaction. This is carried out by heating an aqueous basic solution of phenol with chloroform. The first step is believed to be the formation of a dichloro intermediate. This undergoes hydrolysis, yielding an aldehyde function. Addition of acid liberates the hydroxy aldehyde. Both *o-* and *p-*hydroxy aldehydes are formed, along with some tar.



Steam distillation brings over the *ortho-*isomer, leaving the *para-* behind. This is a useful synthetic method for hydroxy aldehydes.

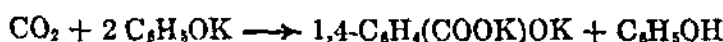
d) With carbon tetrachloride. Heating phenol with carbon tetrachloride and aqueous alcoholic base at 100° (in a sealed tube) yields *p-*hydroxybenzoic acid.



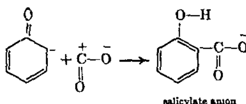
e) *With carbon dioxide.* When carbon dioxide is passed over anhydrous sodium phenoxide (sodium phenate) at 180 to 200°, half of the phenol is converted into disodium salicylate (Kolbe synthesis of salicylic acid).



When potassium phenoxide replaces sodium phenoxide, the corresponding dipotassium salicylate is formed at 100 to 150°, but at higher temperatures this rearranges to the salt of *p*-hydroxybenzoic acid.

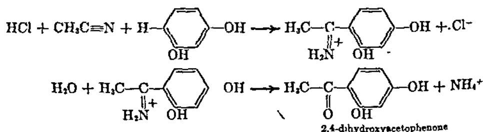


It is believed that the anion of phenol, having a partial negative charge on the *ortho*-carbon atom acts as a nucleophilic reagent, with carbon dioxide reacting in the dipolar form.



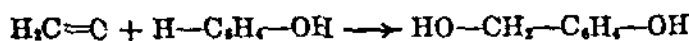
salicylate anion

f) *With nitriles.* A very reactive phenol, for example, resorcinol, reacts with a nitrile and hydrogen chloride in the presence of zinc chloride. The first product, a ketimine salt, undergoes hydrolysis when added to water, yielding a hydroxy ketone.

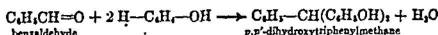


2,4-dihydroxyacetophenone

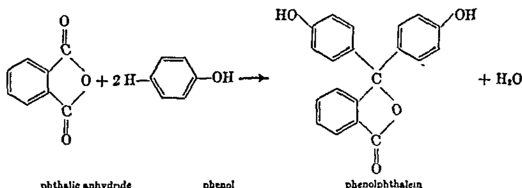
g) *With aldehydes.* Formaldehyde is especially reactive. In the presence of aqueous sodium hydroxide, the condensation product is a mixture of *o*- and *p*-hydroxybenzyl alcohols.



A similar reaction takes place in aqueous ammonia. This is the first step in a series of complicated reactions taking place in the formation of the phenol-formaldehyde type of synthetic resins (p. 282). Benzaldehyde condenses with phenol when the two are heated with a suitable catalyst (sulfuric acid 80-85%).

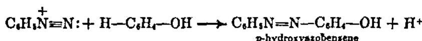


h) With anhydrides. Phthalic anhydride, the anhydride of a dibasic acid, reacts with phenol at 180° in the presence of a suitable catalyst (zinc chloride or sulfuric acid), forming phenolphthalein.



The reaction takes place at the *para*-position only.

i) With diazonium salts. Phenols couple rapidly with diazonium salts (p. 489), producing highly colored hydroxyazo compounds. Preferably reaction takes place at the *para*-position; if this is occupied, then at the *ortho*-position.



MONOHYDRIC PHENOLS

Phenol, Carbolic Acid, C_6H_5OH. One important source is coal tar, which yields 0.2 to 0.5 per cent. An older method of manufacture, developed at the time of World War I, is from benzenesulfonic acid (p. 458). Later, the hydrolysis of chlorobenzene became the important method (p. 452).

Phenol is a colorless solid darkening on exposure to air, owing to oxidation. It is somewhat soluble in water (Table 88) and liquefies on the addition of a small amount of water. On the addition of a little more water a system of two liquid phases results When equilibrium is reached, the lighter phase at 25° has 8.5 per cent phenol and 91.5 per cent water, the heavier phase, 72.8 per cent phenol and 27.2 per cent water. With a rise in temperature the mutual solubilities increase until at 67 5° the two components are miscible in all proportions.

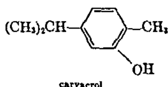
Phenol is an important industrial product From it are obtained a number of pharmaceutical products such as salicylic acid, aspirin, phenolphthalein, and many indicators and dyes; the main use is in the manufacture of synthetic resins of the phenol-formaldehyde type.

Phenol Coefficient. Phenol is a poison. In concentrated form it causes severe burns to tissues. From dilute aqueous solution it may be absorbed through the skin. Phenol is a germicide. Its poisonous and antiseptic properties are due in part to its action in precipitating and coagulating proteins. Homologs of phenol generally have a higher germicidal activity than phenol. This is expressed by the phenol coefficient which is the ratio of the amount of phenol to the amount of some other compound

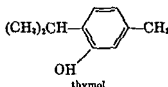
having equal toxic effects on a given organism. Thus, towards *Bacillus typhosus* the following phenol coefficients have been found: cresol mixture about 2, thymol 25, resorcinol 0.3, and *n*-hexylresorcinol 147. A very large number of phenols have been studied from this angle.

Cresols, $CH_3C_6H_4OH$. A mixture of the three cresols is obtained from creosote oil, one of the fractions from coal tar. A mixture of phenols can be extracted from the creosote oil by means of aqueous base. Addition of acid throws out the phenol and cresols. The *ortho*-isomer may be separated from *m*- and *p*-cresol by careful fractional distillation (Table 88). *m*-Cresol may be separated from the others through its greater reactivity. It sulfonates more easily and the sulfonic acid is very soluble in water, whereas the cresols themselves have a low solubility in water. Cresote oil is used in wood preservation. The three cresols may be obtained from the three toluidines by the diazo reaction (Chap. 32). Cresols have higher antiseptic properties than phenol.

Carvacrol and Thymol. These are hydroxy cymenes. They occur naturally in some essential oils, carvacrol in oil of satureia, thymol in oil of thyme and oil of mint. When heated with phosphorus pentoxide carvacrol gives *o*-cresol and propylene, thymol gives *m*-cresol and propylene.



carvacrol



thymol

Thymol is less toxic than phenol (about one fourth) and has a higher phenol coefficient (about 25). Many gargles and mouth washes contain thymol. It is sometimes prescribed for treatment of hookworm.

DIHYDRIC AND TRIHYDRIC PHENOLS

The main interest in dihydric and trihydric phenols arises from their ease of oxidation, a property that makes some of them valuable developers in photography (see p. 509) and makes some excellent for absorbing oxygen (pyrogallol). They are readily soluble in water and give intense colors with dilute aqueous ferric chloride (Table 89).

TABLE 89 | Some Dihydric and Trihydric Phenols

NAME	FORMULA	M.P. °C	B.P. °C	SOLY. IN WATER 20° G./100 G	COLOR WITH $FeCl_3$ SOLN.	K_a
Pyrocatechol	1,2-$C_6H_4(OH)_2$	104.3	246	45	green	1×10^{-10}
Resorcinol	1,3-$C_6H_4(OH)_2$	109.7	281	123	violet	3×10^{-10}
Hydroquinone	1,4-$C_6H_4(OH)_2$	172.9	286	8 [a]	green ppt. → yellow	2×10^{-10}
Pyrogallol	1,2,3-$C_6H_3(OH)_3$	133	309	62 [a]	red	1×10^{-9}
Hydroxyhydroquinone	1,2,4-$C_6H_3(OH)_3$	140.5			greenish brown	
Phloroglucinol	1,3,5-$C_6H_3(OH)_3$	217–219 [b]		1.1	blue violet	3×10^{-9}

[a] At 21°. [b] Dihydrate, ca. 110°

Pyrocatechol, Catechol, Pyrocatechin, 1,2-$C_6H_4(OH)_2$. This is obtained from several sources, including sugar beets, different kinds of eucalpytus, leaves of wild grapes, and many resins. It is present in beech-wood tar in the form of its monomethyl ether, guaiacol, $C_6H_4OHOCH_3$, from which it may be obtained by heating with hydriodic acid. It is formed when catechuic acid (p. 535) undergoes decarboxylation when heated.



$$\underset{\text{catechuic acid}}{C_6H_3COOH(OH)_2} \longrightarrow \underset{\text{pyrocatechol}}{C_6H_4(OH)_2} + CO_2$$

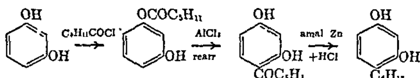
It is prepared from *o*-phenolsulfonic acid or from *o*-bromophenol by fusion with potassium hydroxide but not from chlorophenol, which yields the *meta*-isomer. The higher temperature required in the latter case causes a rearrangement.

Pyrocatechol precipitates metallic gold, silver, and platinum from solutions of their respective salts, and in alkaline solution absorbs oxygen from the air, turning green and then black. The addition of lead ions to pyrocatechol ions (solution of pyrocatechol and sodium hydroxide) throws down an insoluble lead salt, $C_6H_4O_2Pb$. Neither resorcinol nor hydroquinone gives such a precipitate.

Resorcinol, Resorcin, 1,3-$C_6H_4(OH)_2$. This is prepared industrially by fusing *m*-benzenedisulfonic acid with sodium hydroxide. It is also obtained from many other *m*-disubstitution products of benzene, such as the halogenated phenols and phenolsulfonic acid. Even *o*- and *p*-compounds, at sufficiently high temperature, give *m*-dihydroxybenzene, which is formed by a molecular rearrangement at temperatures above 250°. The fusion method is therefore not to be relied upon as a means of determining the structure of aromatic compounds.

The most characteristic reaction of resorcinol is the formation of the dye fluoescein when heated with phthalic anhydride (Chap. 46). Resorcinol is used considerably in the dye industry.

Hexylresorcinol, 2,4-Dihydroxy-*n*-hexylbenzene. This has a phenol coefficient of about 150 against *Bacillus typhosus* and 50 to 100 against *Staphylococcus aureus*. Other derivatives, for example *n*-heptylresorcinol, may have higher values. The hexyl derivative is a component of some antiseptic lotions and sometimes is used in the control of hockworm infections. The method of preparation is typical.



Hydroquinone, 1,4-$C_6H_4(OH)_2$. This occurs in combination with glucose as the glucoside arbutin, from which it is obtained on hydrolysis by dilute acids or by the action of the hydrolytic enzyme, **emulsin.** It gets its name from the fact that it is obtained by the reduction of quinone, $C_6H_4O_2$ (p 543)

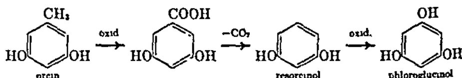
Aqueous solutions of hydroquinone on exposure to air gradually turn brown because of oxidation. On the addition of ferric chloride to aqueous hydroquinone, a dark green solid, quinhydrone (p. 545), separates. More ferric chloride converts it to quinone. Quinone and hydroquinone are easily converted into each other. Hydroquinone is a valuable developer, less active than pyrocatechol, more active than resorcinol. It is manufactured by first oxidizing benzene electrolytically in strong sulfuric acid to quinone and then reducing the latter by sulfurous acid to hydroquinone. Also, aniline is oxidized to quinone by dichromic acid and this is then reduced.

Pyrogallol, Pyrogallic Acid, 1,2,3-$C_6H_3(OH)_3$. This is the most important of the three trihydroxybenzenes. It is obtained by heating gallic acid, 3,4,5-trihydroxybenzoic acid.



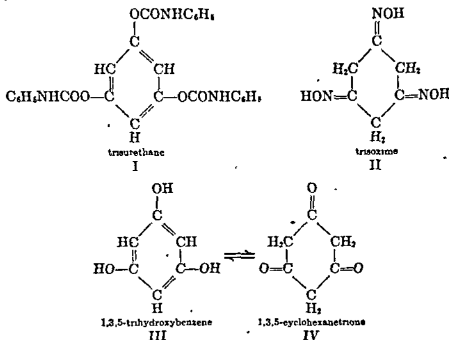
It is a stronger reducing agent than the dihydroxybenzenes. Its alkaline solution readily absorbs oxygen from the air and soon turns brown. Such solutions are used in gas analysis work for the determination of oxygen.

Phloroglucinol, 1,3,5-$C_6H_3(OH)_3$. This is a sweet, colorless crystalline compound obtained by the alkaline hydrolysis of the bitter tasting glucoside, phlorizin, occurring in the root bark of numerous trees, for example, apple, cherry, pear, and plum. Phloroglucinol has been obtained from many other glucosides and from many naturally occurring resins, along with other compounds, usually by alkali fusion. It results from many aromatic compounds when they are fused with a good excess of alkali (potassium hydroxide, usually), for example, phenol, resorcinol, orcinol, and benzenetrisulfonic acid (1,3,5). Its formation from orcin (3,5-dihydroxytoluene) exemplifies both oxidation and decarboxylation, resulting from alkaline fusion.



Hydrogen is evolved during the operation.

Phloroglucinol is tautomeric (p. 325). It acts as a trihydric phenol in forming a trisurethane, I, with phenylisocyanate, and as a triketone in forming a *trisoxime*, II, with hydroxylamine. The tautomeric forms are 1,3,5-trihydroxybenzene, III, and 1,3,5-cyclohexanetrione, IV.

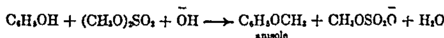


Trihydroxybenzene is the enol form, and triketocyclohexane is the keto form, analogous to the enol and keto forms of ethyl acetoacetate (p. 325), except that here there are three enolic and three ketonic groups. Generally, a ketonic form is more stable than the isomeric enolic form by about 18 kcal. Phenols, in general, are more stable than their tautomeric ketonic forms because of the resonance energy of the benzene ring, about 36 kcal. per mole. In phloroglucinol, however, the ketonic form is favored, because of the energy of ketonization of three groups.

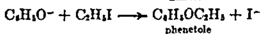
ETHERS

The principal ethers of monohydric phenols are anisole (methyl phenyl ether), $C_6H_5OCH_3$; phenetole (ethyl phenyl ether), $C_6H_5OC_2H_5$; diphenyl ether, $C_6H_5OC_6H_5$; estragole, *p*-methoxyallylbenzene, $CH_2{=}CHCH_2C_6H_4OCH_3$-*p*; and anethole, *p*-methoxypropenylbenzene, $CH_3CH{=}CHC_6H_4OCH_3$-*p*. Anisole is a decomposition product of anethole (see below) when the latter is heated sufficiently.

Ethers having an alkoxyl group usually can be obtained from the corresponding phenol by the action of an alkylating agent under basic conditions, or from a salt of the phenol.

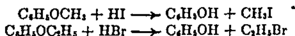


$$C_6H_5OH + (CH_3O)_2SO_2 + \bar{O}H \longrightarrow \underset{\text{anisole}}{C_6H_5OCH_3} + CH_3OSO_2\bar{O} + H_2O$$



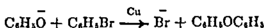
$$C_6H_5O^- + C_2H_5I \longrightarrow \underset{\text{phenetole}}{C_6H_5OC_2H_5} + I^-$$

Anisole, phenetole, and many other ethers are cleaved when heated with concentrated hydriodic acid or hydrogen bromide in glacial acetic acid.



$$C_6H_5OCH_3 + HI \longrightarrow C_6H_5OH + CH_3I$$
$$C_6H_5OC_2H_5 + HBr \longrightarrow C_6H_5OH + C_2H_5Br$$

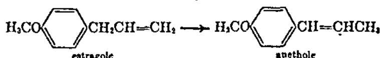
Diphenyl ether is formed in a typical Williamson reaction when potassium phenoxide and bromobenzene are heated to about 210° in the presence of copper powder.



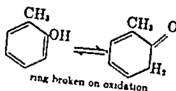
$$C_6H_5\bar{O} + C_6H_5Br \xrightarrow{Cu} \bar{B}r + C_6H_5OC_6H_5$$

The ether is a by-product in the manufacture of phenol from chlorobenzene at 300 to 350°, owing to a similar reaction.

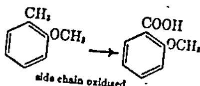
Anethole has a characteristic aniselike aroma and is used in the manufacture of some perfumes and liquors. Estragole has a similar odor. An interesting reaction takes place when this compound is heated with alcoholic alkali, a reaction characteristic of many allyl compounds. The double bond shifts towards the ring.



An ether is much more resistant to oxidation than the corresponding phenols Whereas *o*-cresol is rapidly oxidized by permanganate with destruction of the ring, *o*-cresyl methyl ether is much more resistant The methyl group is oxidized to carboxyl, yielding *o*-methoxybenzoic acid. Ready oxidation of the phenol is sometimes explained as a result of tautomerism.



ring broken on oxidation



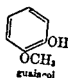
side chain oxidized

TABLE 90 | Some Phenolic Ethers

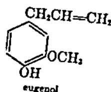
	M.P. °C	B.P °C	OCCURRENCE
Anisole	−37	153	
Phenetole	−33	172	
Diphenyl ether			
Estragole		215	oil of aniseed, oil of fennel
Anethole	22–23		oil of aniseed, oil of fennel
Guaiacol	28	205	*
Eugenol		252	oil of cloves
Isoeugenol	33	261	oil of nutmeg, ilang-ilang oil
Chavibetol	8 5	254	betel nut leaves
Safrole	11	233	oil of sassafras, oil of camphor
Isosafrole		253	ilang-ilang oil

* In the distillate obtained by heating guaiacum resin or beach wood resin.

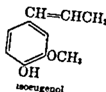
Many ethers of polyhydric phenols occur naturally (Table 90). The structures of some of these are shown.



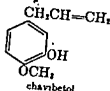
guaiacol



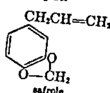
eugenol



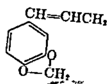
isoeugenol



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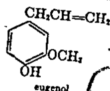


safrole

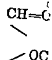


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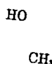
Guaiacol is converted to vanillin in ... -Tiemann rea...). Eugenol has the characteristic odor of clov... eated with ... nverted to isoeugenol. Controlled oxidation o... nillin.



eugenol



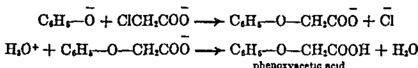
...ugenol



Safrole is conver... le w... yields piperonal on... tion ... i sometimes called a ... g.

they are cyclic formals of dihydric phenols. In some cases, piperonal (p. 522) for example, the ring is cleaved when the compound is heated with aqueous acid, yielding formaldehyde and the corresponding dihydridic compound. However, isosafrole may undergo polymerization under acidic conditions.

Phenoxyacetic Acids. These are formed in a reaction between sodium salts of phenols and sodium chloroacetate.



$$C_6H_5\text{—}\bar{O} + ClCH_2CO\bar{O} \longrightarrow C_6H_5\text{—}O\text{—}CH_2CO\bar{O} + \bar{Cl}$$

$$H_3O^+ + C_6H_5\text{—}O\text{—}CH_2CO\bar{O} \longrightarrow \underset{\text{phenoxyacetic acid}}{C_6H_5\text{—}O\text{—}CH_2COOH} + H_2O$$

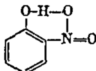
Addition of a strong acid to an aqueous solution of the resulting salt precipitates the phenoxyacetic acid. Compounds of this type are useful in the identification of phenols, owing to ease of preparation and purification, readiness with which they can be converted to other solid derivatives, as for example amides, and easy titratability.

A derivative, 2,4-dichlorophenoxyacetic acid (2,4-D), made with 2,4-dichlorophenol, has the remarkable property of being able to kill broad leafed plants while not harming grasses. It is used as a weed killer. Other similar derivatives have like properties.

Essential Oils. An essential oil is so called because it possesses the essence, or characteristic quality (such as perfume, scent, flavor), of the plant from which it has been separated. It is to be distinguished from a **mineral oil,** *i.e.*, a petroleum, and a **vegetable** or **edible oil,** *i.e.*, a glyceride. The essential oil may consist of one component mainly, as oil of wintergreen, or it may be a mixture of two or more substances, as most essential oils are. The usual compounds are aliphatic aldehydes or esters; aromatic alcohols, ethers, aldehydes, acids, or esters of aromatic acids; terpenes or oxygen derivatives of the terpenes. A number of essential oils are mentioned in Tables 90 and 91 (p. 522). In the former table a number of phenolic ethers are shown, and in the latter, a number of aromatic aldehydes.

NITROPHENOLS

Nitrophenols, $C_6H_4OHNO_2$. A mixture of *o*- and *p*-nitrophenol results from nitration of phenol. A dilute nitric acid can bring about nitration. These same isomers can be obtained from the corresponding chloro or bromonitrobenzenes by heating with alcoholic base at 120°. The isomers are readily separated by steam distillation; *o*-nitrophenol distils with steam; the *m*- and *p*-nitrophenols do not. The difference is explained by chelation, owing to hydrogen bonding between the hydroxyl group and a nitro group in the *ortho*- but not in the *meta*- or *para*-positions.



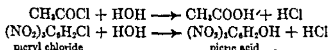
The *ortho*-isomer has a penetrating, phenollike odor, the *meta* and *para* little or no odor. The *ortho*- and *meta*-isomers are yellow; the *para*- is colorless They are stronger acids than phenol and decompose hot solutions of sodium carbonate.

2,4-Dinitrophenol, $C_6H_3OH(NO_2)_2$. This is a yellow solid. It has the remarkable property of greatly increasing the metabolic rate when it is taken internally. Three or four milligrams per kilo of body weight raises the body temperature above normal.

Picric Acid, 2,4,6-Trinitrophenol, $C_6H_2OH(NO_2)_3$. This is obtained by nitrating phenol with a mixture of concentrated sulfuric and nitric acids. Many substances, for example, certain proteins and resins, yield picric acid with concentrated nitric acid It is also obtained by the hydrolysis of 2,4,6-trinitrochlorobenzene. Picric acid is yellow in color, is poisonous, has a bitter taste, and decomposes explosively when heated rapidly. It dyes silk and wool a yellow color.

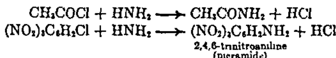
Picric acid is an illustration of an organic acid not having a carboxyl group. The reactions of compounds related to picric acid are analogous to the reactions of compounds related to acetic acid.

1 *Hydrolysis of acid chlorides.*



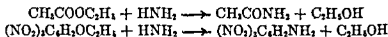
$$CH_3COCl + HOH \longrightarrow CH_3COOH + HCl$$
$$\underset{\text{picryl chloride}}{(NO_2)_3C_6H_2Cl} + HOH \longrightarrow \underset{\text{picric acid}}{(NO_2)_3C_6H_2OH} + HCl$$

2. *Ammonolysis of acid chlorides.*



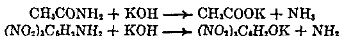
$$CH_3COCl + HNH_2 \longrightarrow CH_3CONH_2 + HCl$$
$$(NO_2)_3C_6H_2Cl + HNH_2 \longrightarrow \underset{\substack{\text{2,4,6-trinitroaniline}\\ \text{(picramide)}}}{(NO_2)_3C_6H_2NH_2} + HCl$$

3. *Ammonolysis of esters (ethers).*



$$CH_3COOC_2H_5 + HNH_2 \longrightarrow CH_3CONH_2 + C_2H_5OH$$
$$(NO_2)_3C_6H_2OC_2H_5 + HNH_2 \longrightarrow (NO_2)_3C_6H_2NH_2 + C_2H_5OH$$

4 *Hydrolysis of amides.*



$$CH_3CONH_2 + KOH \longrightarrow CH_3COOK + NH_3$$
$$(NO_2)_3C_6H_2NH_2 + KOH \longrightarrow (NO_2)_3C_6H_2OK + NH_3$$

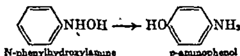
The trinitrophenyl radical, $(NO_2)_3C_6H_2$, is strongly negative, owing to the presence of the three nitro groups. It brings about the same type of reactions as the acetyl group does, but these are more sluggish.

Picric acid and its salts are powerful explosives. The ammonium salt, lyddite, was formerly employed extensively as a high explosive in shells, but has been largely replaced by trinitrotoluene or other explosives.

Picric acid forms addition compounds with many aromatic hydrocarbons and with a large number of their derivatives, especially the amines. These addition compounds crystallize well and have fairly sharp melting points They are valuable aids in identification of some tertiary amines and aromatic hydrocarbons.

AMINO PHENOLS

Amino phenols may be prepared by reduction of the corresponding nitrophenols, but often the yields are poor. Conversion of diamines to aminophenols via the *diazo* reaction can be accomplished for the *para*-isomer in normal fashion and for the *meta*-isomer when there is large excess of acid (preferably hydrochloric) and its concentration is relatively high, to prevent coupling. The *ortho*-isomer undergoes ring closure. Some aminophenols with the amino group *para* to the hydroxyl group can be obtained by rearrangement of the proper substituted hydroxylamine, similar to that of N-phenylhydroxylamine (p. 465).



Industrially *p*-aminophenol is produced by the electrolytic reduction of nitrobenzene in sulfuric acid; here the intermediate, N-phenylhydroxylamine, undergoes rearrangement before reduction and the sulfate crystallizes out.

Amino phenols are amphoteric, but are only weakly acidic and weakly basic. They are excellent reducing agents, and like di- and polyhydric phenols and diaminobenzenes, are used in photography, because they reduce silver halide to metallic silver. Many developers have special trade names.

Adurol, chlorohydroquinone, or bromohydroquinone
Amidol, a salt of 2,4-diaminophenol
Elon, *p*-N-methylaminophenol sulfate
Glycin, *p*-hydroxy-N-phenylglycine
Metol, same as Elon
Rodinal, *p*-aminophenol hydrosulfate

A good developer has, in positions *ortho* or *para* to each other, two functional groups of the following types: hydroxyl, amino, and mono alkylamino radicals. They may be the same or different. It is just these combinations that render the molecule susceptible to easy oxidation. The first step in the oxidation reaction is believed to be the formation of a quinone, a quinone diimine, or a quinone monoimine (p. 545) The reaction actually is more complicated, because quinone and hydroquinone combine to form quinhydrone.

A number of aliphatic ethers of 2-amino-4-nitrophenol are sweet. The *n*-propyl ether, the sweetest one, is 5000 times as sweet as sucrose It is said to be the sweetest substance yet discovered It is prepared from 2,4-dinitrophenyl propyl ether by partial reduction with sodium disulfide, Na_2S_2.

Identification of Phenols. For detecting phenols the most useful reagents are

bromine water gives precipitates (p. 497). However, aniline and many substituted

(p. 507). Determination of the bromine absorption number, by the use of standard bromine or standard bromide-bromate solution, gives an indication of how many of the *ortho-* and *para-*positions are unoccupied.

PROBLEMS

1. Indicate the operations and conditions for a practical synthesis of the following, reasonably pure, from benzene.

a) *m*-nitrophenol
b) *p*-nitrophenol
c) *o*-aminophenol
d) *o*-fluoroanisole
e) *m*-chlorophenol
f) *p*-bromophenol
g) *o*-nitrophenetole
h) *m*-nitroanisole
i) *p*-nitro-*n*-butoxybenzene
j) *o*-iodoanisole
k) *m*-hydroxybenzonitrile
l) *p*-fluorophenetole
m) *o*-acetamidophenol
n) *m*-acetamidophenetole

o) *p*-amino-N-methylaniline
p) *o*-hydroxybenzenesulfonic acid
q) *m*-hydroxybenzenesulfonic acid
r) *p*-hydroxybenzenesulfonic acid
s) 2-sulfo-4-hydroxyacetanilide
t) 2-bromo-4-hydroxyacetanilide
u) 2-hydroxy-4-sulfoacetanilide
v) 2-sulfo-4-nitrophenol
w) 3-sulfo-4-aminophenol
x) 3-bromo-4-aminophenol
y) *p*-nitrophenoxyacetic acid
z) *m*-bromophenoxyacetic acid

2. Ditto, but from toluene

a) methyl *o*-tolyl ether
b) ethyl *m*-tolyl ether
c) *p*-tolyl acetate
d) *o*-cresyl benzoate
e) *m*-cresyl acetate
f) *p*-cresyl phosphate
g) *o*-thiocresol
h) *m*-thiocresol
i) *p*-thiocresol
j) ethyl *o*-tolyl sulfide
k) *n*-propyl *m*-tolyl sulfide
l) *n*-butyl *p*-tolyl sulfide
m) *o*-hydroxy-*p*-nitrotoluene
n) *o*-nitro-*p*-hydroxytoluene
o) *o*-hydroxy-*p*-acetamidotoluene
p) *o*-hydroxy-*p*-fluorotoluene
q) *o*-bromo-*p*-ethoxytoluene
r) *o*-hydroxy-*p*-bromotoluene
s) *o*-ethoxy-*p*-iodotoluene
t) *o*-bromo-*p*-fluorotoluene
u) *m*-nitro-*p*-hydroxytoluene
v) *o*-hydroxy-*p*-cyanotoluene
w) *o*-chloro-*p*-methoxytoluene
x) *m*-bromo-*p*-hydroxytoluene
y) *o*-iodo-*p*-*n*-propoxytoluene
z) 3,4-dibromotoluene

3. Describe a convenient chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) *o*-nitrophenol and *o*-nitrotoluene
b) phenetole and *p*-ethylphenol
c) phenetole and ethylbenzene
d) phenetole and diphenyl ether
e) *o*-cresol and *o*-xylene
f) *m*-cresol and *m*-xylene
g) *o*-chlorophenol and *o*-dichlorobenzene
h) *p*-chlorophenol and *p*-chloroanisole
i) *p*-cresol and *p*-cymene
j) *p*-cresol and phenetole
k) *p*-cresol and hydroquinone
l) resorcinol and hydroquinone
m) *o*-nitrophenol and *o*-aminophenol
n) *p*-bromophenol and *p*-bromotoluene
o) *p*-nitrophenol and *p*-nitrotoluene
p) *o*-nitrophenol and *m*-nitro-*p*-hydroxytoluene
q) *m*-nitro-*p*-hydroxytoluene and *p*-methyphenylhydroxylamine
r) *o*-cresol and pyrocatechol
s) *m*-nitrophenol and 2,4-dinitrophenol
t) carvacrol and cymene

4. Describe a convenient procedure including reagent, solvent, and operation (distillation, filtration, etc.) for conveniently separating the components so as to recover one essentially quantitatively and free of the other.

a) phenol and phenetole
b) *p*-chlorophenol and *o*-nitrotoluene
c) *o*-toluidine and benzyl alcohol
d) aniline and *p*-cymene
e) thymol and *p*-chloroaniline
f) anisole and cumene
g) anisole and bromobenzene
h) phenol and *o*-dichlorobenzene
i) *p*-cresol and durene
j) thymol and *o*-bromoaniline
k) *p*-chlorophenol and naphthalene
l) *o*-chlorophenol and *n*-heptyl alcohol

o) p-amino-N-methylaniline
p) o-hydroxybenzenesulfonic acid
q) m-hydroxybenzenesulfonic acid
r) p-hydroxybenzenesulfonic acid
s) 2-sulfo-4-hydroxyacetanilide
t) 2-bromo-4-hydroxyacetanilide

2. Ditto, but from toluene

a) methyl o-tolyl ether
b) ethyl m-tolyl ether
c) p-tolyl acetate
d) o-cresyl benzoate
e) m-cresyl acetate
f) p-cresyl phosphate
g) o-thiocresol
h) m-thiocresol
i) p-thiocresol
j) ethyl o-tolyl sulfide
k) n-propyl m-tolyl sulfide
l) n-butyl p-tolyl sulfide
m) o-hydroxy-p-nitrotoluene

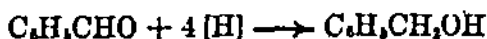
3. Describe a convenient chemical test (
detectable change) that serves to distinguis

a) o-nitrophenol and o-nitrotoluene
b) phenetole and p-ethylphenol
c) phenetole and ethylbenzene
d) phenetole and diphenyl ether
e) o-cresol and o-xylene
f) m-cresol and m-xylene
g) o-chlorophenol and o-dichlorobenze
h) p-chlorophenol and p-chloroanisole
i) p-cresol and p-cymene
j) p-cresol and phenetole
k) p-cresol and hydroquinone
l) resorcinol and hydroquinone
m) o-nitrophenol and o-aminopheno
n) p-bromophenol and p-bromotol
o) p-nitrophenol and p-nitrotoluen
p) o-nitrophenol and m-nitro-p-hy
q) m-nitro-p-hydroxytoluene and
r) o-cresol and pyrocatechol
s) m-nitrophenol and 2,4-dinitr
t) carvacrol and cymene

4. Describe a convenient proc
tion, filtration, etc.) for convenie
tially quantitatively and free of

a) phenol and phenetole
b) p-chlorophenol and o-nit
c) o-toluidine and benzyl a
d) aniline and p-cymene
e) thymol and p-chloroar
f) anisole and cumene

3. *Reduction of aromatic acids.* An older method is electrolytic reduction, which is more effective for aromatic than for aliphatic acids. Lithium aluminum hydride reduces acids to alcohols, also.



$$C_6H_5CHO + 4[H] \longrightarrow C_6H_5CH_2OH$$

4. *Dismutation of aldehydes; the Cannizzaro reaction.* This is a convenient laboratory method for benzyl alcohol and numerous derivatives (p. 517).

5. *Grignard synthesis.* This is an especially valuable method (p. 138).

Reactions. Aromatic alcohols resemble aliphatic alcohols chemically Primary alcohols can be oxidized to aldehydes or acids, secondary to ketones. Secondary and tertiary alcohols, ArCHOHAlk and $ArCOHAlk_2$, respectively, often lose water when they are being distilled at atmospheric pressure, forming an unsaturated hydrocarbon in which the olefinic double bond is conjugated with the ring.

Replacement of the hydroxyl group takes place readily. For example, benzyl alcohol reacts with concentrated hydrohalic acids, as well as with the anhydrous acids, forming the corresponding benzyl halide. It reacts with benzene (sulfuric acid or aluminum chloride as the catalyst), forming diphenylmethane.



$$C_6H_5—CH_2—OH + C_6H_6 \longrightarrow C_6H_5—CH_2—C_6H_5 + H_2O$$

Direct substitution of alcohols usually is not feasible because of side reactions. Benzyl alcohol, for example, undergoes resinification with concentrated sulfuric acid; however, with a small amount, or with dilute sulfuric acid, dibenzyl ether is formed on heating. Nitric acid causes oxidation to benzaldehyde, and halogens also may bring about oxidation as well as substitution on the side chain.

Benzyl alcohol, $C_6H_5CH_2OH$, has a local anesthetic action and is used some in ointments. This property is shown also in certain derivatives, for example, ephedrine and adrenalin (Chap. 45). Benzylcarbinol (β-phenylethyl alcohol, β-phenylethanol) also has anesthetic properties.

ALDEHYDES AND KETONES

The important aromatic aldehydes and ketones are those in which the carbonyl group is attached to ring carbon. In general they resemble the aliphatic oxo compounds except that the aldehydes differ in their behavior with strong bases, ammonia, and oxidizing agents. Aldehydes and ketones in which the oxo group is separated from the benzene ring resemble more closely the aliphatic compounds.

Aromatic aldehydes occur in many natural products, such as resins and essential oils, and it is largely to the aldehydes that these products owe their characteristic aroma or essence. Some ketones also occur naturally.

Preparation of Oxo Compounds. Many of the methods of preparing the aliphatic compounds are useful here (pp. 255–258), as for example the first seven mentioned below. The rest are applicable to aromatic compounds.

CHAPTER 34

Aromatic Alcohols, Aldehydes, Ketones

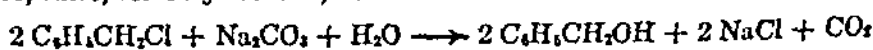
ALCOHOLS

Aromatic alcohols may be regarded as hydroxyl derivatives of aromatic hydrocarbons with the hydroxyl group on a side chain, or as aliphatic alcohols having one or more aromatic rings in the molecule. The simplest aromatic alcohol, benzyl alcohol, $C_6H_5CH_2OH$, may be designated as α-hydroxytoluene or as phenylcarbinol. Secondary alcohols are of two types, *viz.*, ArAlkCHOH and Ar_2CHOH; tertiary, three types, $ArAlk_2COH$, $Ar_2AlkCOH$, and Ar_3COH. Some of these are described in Chapter 37.

Many of these alcohols and many more of their esters have pleasant, fragrant odors. Some are found naturally, for example, benzyl alcohol in Peru and Tolu balsams, β-phenylethyl alcohol (β-hydroxyethylbenzene), $C_6H_5CH_2CH_2OH$, in oil of rose and oil of neroli, γ-phenyl-*n*-propyl alcohol (γ-hydroxy-*n*-propylbenzene), $C_6H_5CH_2CH_2CH_2OH$ in a number of balsams and resins. It has an odor resembling that of hyacinths. Cinnamyl alcohol, $C_6H_5CH{=}CHCH_2OH$, occurs in oil of cinnamon. Benzyl acetate is found in oil of jasmine, oil of hyacinth, and in other oils, and is often an ingredient of perfumes. Other esters also are used, for example, benzoates and cinnamates.

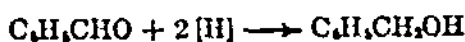
Preparation. The methods for alcohols in general (Chap. 10) are applicable to aromatic alcohols. However, side reactions may be more troublesome here as, for example, formation of a double bond when it is conjugated with the ring, or reduction to the hydrocarbon.

1. *Hydrolysis of halogen derivatives.* The most reactive are those of the benzyl type (p. 451). Hydrolysis may be done by heating with water, but usually a base is added, such as sodium hydroxide, sodium carbonate, sodium acetate, lime, lead hydroxide, etc.



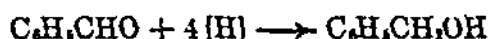
$$2\,C_6H_5CH_2Cl + Na_2CO_3 + H_2O \longrightarrow 2\,C_6H_5CH_2OH + 2\,NaCl + CO_2$$

2. *Reduction of aromatic aldehydes, ketones, and esters.* An older method is the one with sodium amalgam and water, a newer, with lithium aluminum hydride (p. 133).



$$C_6H_5CHO + 2\,[H] \longrightarrow C_6H_5CH_2OH$$

3. *Reduction of aromatic acids.* An older method is electrolytic reduction, which is more effective for aromatic than for aliphatic acids. Lithium aluminum hydride reduces acids to alcohols, also.



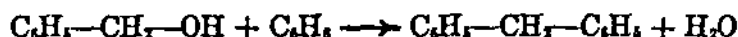
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ALDEHYDES AND KETONES

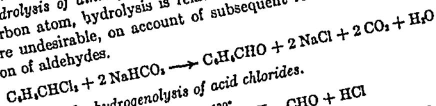
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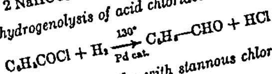
1. *Mild oxidation of the corresponding alcohol.*

2. *Hydrolysis of dihalogeno derivatives.* When the halogen atoms are on an α-carbon atom, hydrolysis is relatively easy. Strongly basic conditions often are undesirable, on account of subsequent reactions, particularly dismutation of aldehydes.



$$C_6H_5CHCl_2 + 2\,NaHCO_3 \longrightarrow C_6H_5CHO + 2\,NaCl + 2\,CO_2 + H_2O$$

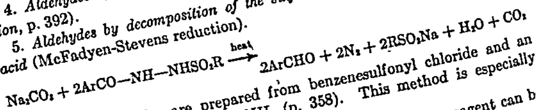
3. *Aldehydes, by hydrogenolysis of acid chlorides.*



$$C_6H_5COCl + H_2 \xrightarrow[\text{Pd cat.}]{130^\circ} C_6H_5{-}CHO + HCl$$

4. *Aldehydes by reduction of nitriles with stannous chloride* (*Stephens reduction*, p. 392).

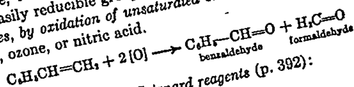
5. *Aldehydes by decomposition of the sulfonhydrazides of the corresponding acid* (McFadyen-Stevens reduction).



$$Na_2CO_3 + 2ArCO{-}NH{-}NHSO_2R \xrightarrow{\text{heat}} 2ArCHO + 2N_2 + 2RSO_2Na + H_2O + CO_2$$

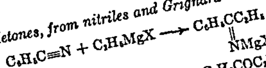
The sulfonhydrazides are prepared from benzenesulfonyl chloride and an acyl hydrazide, Ar—CO—NH—NH$_2$ (p. 358). This method is especially useful when easily reducible groups are present.

6. *Aldehydes, by oxidation of unsaturated side chains.* The reagent can be chromic acid, ozone, or nitric acid.

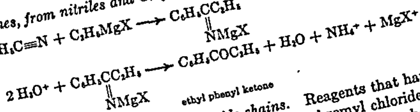


$$C_6H_5CH{=}CH_2 + 2\,[O] \longrightarrow \underset{\text{benzaldehyde}}{C_6H_5{-}CH{=}O} + \underset{\text{formaldehyde}}{H_2C{=}O}$$

7. *Ketones, from nitriles and Grignard reagents* (p. 392):



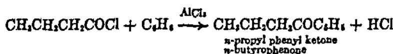
$$C_6H_5C{\equiv}N + C_2H_5MgX \longrightarrow C_6H_5\underset{\underset{\textstyle NMgX}{\|}}{C}C_2H_5$$



$$2\,H_3O^+ + C_6H_5\underset{\underset{\textstyle NMgX}{\|}}{C}C_2H_5 \longrightarrow \underset{\text{ethyl phenyl ketone}}{C_6H_5COC_2H_5} + H_2O + NH_4^+ + MgX^+$$

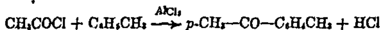
8. *Aldehydes, by oxidation of methyl side chains.* Reagents that have been used are manganese dioxide with sulfuric acid, and chromyl chloride (Etard synthesis). The latter forms an addition product with a hydrocarbon; toluene, for example, gives $C_6H_5CH_3 \cdot 2\,CrO_2Cl_2$. The aldehyde is formed on the addition of water.

9. *The Friedel-Crafts synthesis.* This is about the most important method of ketone synthesis. It can be used also for aldehydes. Acyl chlorides react, in the presence of aluminum chloride, with benzene or with numerous derivatives. Reaction does not take place if there is a strongly deactivating group on the benzene ring, for example, nitro or acyl, unless there also is a strongly activating group. Thus, ordinarily, only one acyl group enters the molecule. With some activating groups other reactions are possible, for example migration of alkyl groups and removal of alkyl groups from ethers.

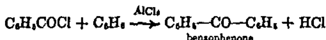


The carbon chain is not altered. Thus a long, normal carbon chain can be attached to the benzene ring.

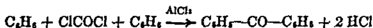
A *para*-isomer is the main product if an alkyl, halogeno, alkoxyl, or hydroxyl group is already present.



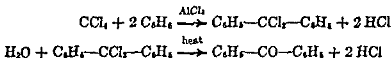
Chlorides of aromatic acids yield purely aromatic ketones.



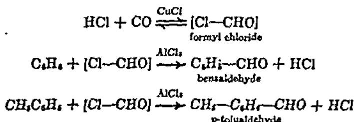
Phosgene also yields aromatic ketones.



Carbon tetrachloride yields a dichloro compound under carefully controlled conditions and this can be hydrolyzed to an aromatic ketone.



Aldehydes are obtained by the action of carbon monoxide, hydrogen chloride, cuprous chloride, and aluminum chloride (Gattermann-Koch method). In the presence of cuprous chloride the mixture of the two gases reacts as if it were formyl chloride, which is unstable under ordinary conditions. The reaction with benzene requires heating to 60°, preferably under pressure. Toluene or any alkyl benzene gives the *para*-isomer.



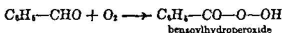
10. *Hydroxy aldehydes*, by the action of hydrogen cyanide under proper conditions (p. 499) or by the Reimer-Tiemann reaction (p. 499). From phenol, a mixture of *o*- and *p*-hydroxybenzaldehydes is obtained (p. 522). The isomers can be separated by steam distillation. The *ortho* distils with steam, the *para* does not.

11. *Hydroxyketones*, by reaction of certain phenols with aliphatic nitriles and hydrogen chloride (p. 500), or by rearrangement of esters of phenols (p. 496).

Reactions of Aromatic Aldehydes and Ketones. These differ in many respects from those of aliphatic compounds. A number of differences are mentioned here, before the reactions of benzaldehyde, a typical aldehyde, and acetophenone, a typical ketone, are described. Reactions that are markedly different are: *oxidation*, aromatic aldehydes in general are less easily oxidized, except they undergo autoxidation (with oxygen) more readily, and both aldehydes and ketones, under vigorous oxidation, yield benzoic acid, no matter how long the side chain; *Fehling's solution*, not reduced when the aldehyde group is attached to the ring; *silver ammonia ion*, reduced by an aldehyde under carefully controlled conditions; *reduction*, a hydrocarbon often results, rather than an alcohol; *dismutation*, characteristic of aldehydes having the carbonyl group next to the ring; *sodium bisulfite*, aldehydes react, but not ketones with the carbonyl group adjacent to the ring; *benzoin condensation*, characteristic of aldehydes having the carbonyl group next to the ring. *Reactions on the ring* are those of substitution, and the products are predominately *meta*, owing to the deactivating influence of an oxo group adjacent to the ring.

The main reactions of aldehydes are those of the aldehyde group.

1. *Oxidation* The most interesting reaction is that of **autoxidation,** that is, spontaneous oxidation by oxygen. Benzaldehyde is rapidly oxidized to benzoic acid. The reaction proceeds in steps, and the first product is perbenzoic acid (peroxybenzoic acid, benzoylhydroperoxide), resulting from an addition reaction between benzaldehyde and oxygen.



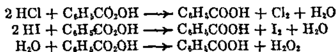
$$C_6H_5{-}CHO + O_2 \longrightarrow \underset{\text{benzoylhydroperoxide}}{C_6H_5{-}CO{-}O{-}OH}$$

Benzoylhydroperoxide is an active oxidizing agent and rapidly oxidizes benzaldehyde to benzoic acid, by being itself reduced to benzoic acid.



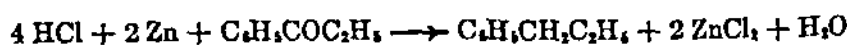
$$C_6H_5CO{-}O{-}OH + C_6H_5CHO \longrightarrow 2\,C_6H_5COOH$$

Peroxybenzoic acid liberates chlorine from hydrogen chloride and iodine from hydrogen iodide, and reacts slowly with water, forming hydrogen peroxide.



$$2\,HCl + C_6H_5CO_2OH \longrightarrow C_6H_5COOH + Cl_2 + H_2O$$
$$2\,HI + C_6H_5CO_2OH \longrightarrow C_6H_5COOH + I_2 + H_2O$$
$$H_2O + C_6H_5CO_2OH \longrightarrow C_6H_5COOH + H_2O_2$$

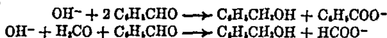
2. *Reduction.* Reducing agents like sodium and alcohol or lithium aluminum hydride reduce aldehydes and ketones to the corresponding alcohols (p. 512). However, in the reduction of aldehydes, a buffer must be added in the first case, to prevent the mixture from becoming basic. Amalgamated zinc and hydrochloric acid cause reduction to the hydrocarbon stage (Clemmensen reduction).



$$4\,HCl + 2\,Zn + C_6H_5COC_2H_5 \longrightarrow C_6H_5CH_2C_2H_5 + 2\,ZnCl_2 + H_2O$$

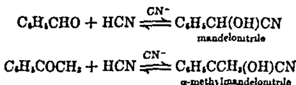
This is a generally useful method for obtaining a normal alkyl side chain, by reduction of the corresponding ketone side chain attached by a Friedel-Crafts reaction (p. 514).

3. *Dismutation of aldehydes.* The Cannizzaro reaction proceeds quit smoothly when the aldehyde group is attached to the benzene ring, becaus no aldol condensation can take place in the absence of a labile α-hydroge atom. When alcohol is desired, formaldehyde is added, to increase the yield in a so-called "crossed" Cannizzaro reaction.



$$OH^- + 2\,C_6H_5CHO \longrightarrow C_6H_5CH_2OH + C_6H_5COO^-$$
$$OH^- + H_2CO + C_6H_5CHO \longrightarrow C_6H_5CH_2OH + HCOO^-$$

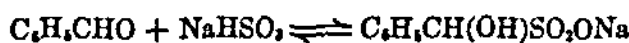
4. *Addition reactions.* Hydrogen cyanide adds well to aldehydes, but onl incompletely to ketones.



$$C_6H_5CHO + HCN \underset{}{\overset{CN^-}{\rightleftharpoons}} \underset{\text{mandelonitrile}}{C_6H_5CH(OH)CN}$$
$$C_6H_5COCH_3 + HCN \overset{CN^-}{\rightleftharpoons} \underset{\alpha\text{-methylmandelonitrile}}{C_6H_5CCH_3(OH)CN}$$

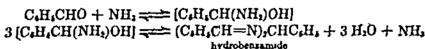
The equilibrium constant of the first reaction in alcoholic solution is about 200 and of the second, 0.8.

Sodium bisulfite adds to aldehydes and to those ketones whose carbonyl group is not attached directly to the benzene ring.



$$C_6H_5CHO + NaHSO_3 \rightleftharpoons C_6H_5CH(OH)SO_2ONa$$

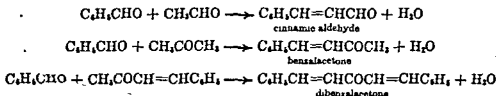
5. *Condensation with nitrogen compounds: oximes, etc.* Aldehydes and ketones form oximes with hydroxylamine; hydrazones with hydrazine and substituted hydrazines, in particular 2,4-dinitrophenylhydrazine (p. 490). Aldehydes form Schiff's bases with aniline and other aromatic primary amines. Benzaldehyde forms **hydrobenzamide** with ammonia. This reaction probably proceeds through the amino alcohol, by loss of water and ammonia.



$$C_6H_5CHO + NH_3 \rightleftharpoons [C_6H_5CH(NH_2)OH]$$
$$3\,[C_6H_5CH(NH_2)OH] \rightleftharpoons \underset{\text{hydrobenzamide}}{(C_6H_5CH{=}N)_2CHC_6H_5} + 3\,H_2O + NH_3$$

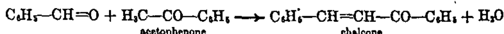
The reaction is reversible and benzaldehyde can be regenerated by the action of hydrochloric acid.

6. *Condensations: a) With oxo compounds having a labile α-hydrogen atom:* 1) *Aldehydes with aldehydes and ketones.* Aldol type condensations take place readily under basic conditions, and some of the aldols are known, for example, 3-*o*-nitrophenyl-3-hydroxypropanal. Usually, however, water is eliminated and the product is an unsaturated compound.



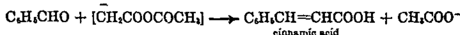
$$C_6H_5CHO + CH_3CHO \longrightarrow \underset{\text{cinnamic aldehyde}}{C_6H_5CH{=}CHCHO} + H_2O$$
$$C_6H_5CHO + CH_3COCH_3 \longrightarrow \underset{\text{benzalacetone}}{C_6H_5CH{=}CHCOCH_3} + H_2O$$
$$C_6H_5CHO + CH_3COCH{=}CHC_6H_5 \longrightarrow \underset{\text{dibenzalacetone}}{C_6H_5CH{=}CHCOCH{=}CHC_6H_5} + H_2O$$

The reaction with aldehyde takes place in about a week at room temperature in dilute aqueous solution having about 0.1 per cent sodium hydroxide; the one with acetone by stirring the reactants for a number of hours in more concentrated solutions. Dismutation takes place also. The aromatic aldehyde furnishes the positive carbon atom, the aliphatic, the nucleophilic carbon, by removal of the labile hydrogen atom by the action of the basic catalyst (p. 275). Benzaldehyde also condenses with aromatic ketones in the presence of aluminum chloride.



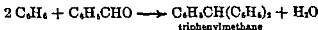
2) *Aldehydes with anhydrides; the Perkin reaction.* This takes place when the aldehyde, sodium acetate, and acetic anhydride are heated for some time at refluxing temperature.

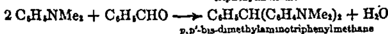


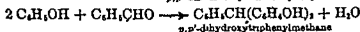


Sodium acetate is the basic catalyst for the reaction by removing a proton from the α-carbon atom of the anhydride. The nucleophilic carbon atom of the resulting anion attacks the carbon atom of the aldehyde, forming an enol ion which, at the elevated temperature, is cleaved to cinnamic acid and acetate ion (or cinnamate ion and acetic acid). The reaction is fairly general and is a convenient method of introducing a three-carbon side chain.

b) Aldehydes with aromatic compounds. Benzaldehyde reacts with benzene at 60 to 80° in the presence of ferric chloride or aluminum chloride; with dimethylaniline at 100° in the presence of zinc chloride; and with phenol, on cooling, in the presence of sulfuric acid, about 80 per cent.

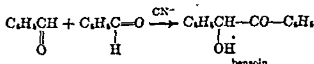






The last two products are of interest in connection with dyes (Chap. 46).

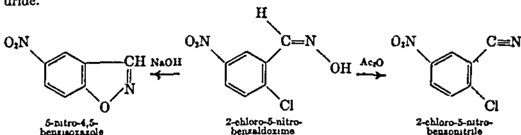
c) Aldehydes with themselves; the benzoin condensation. Many aromatic aldehydes undergo, when in contact with potassium cyanide, an intermolecular condensation that leads to the formation of a hydroxy ketone (benzoin).



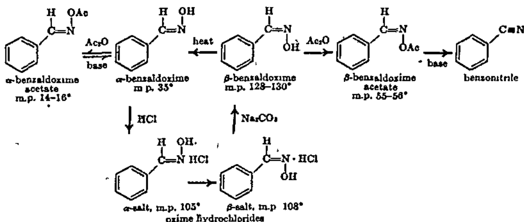
Oximes; Stereochemistry. Oximes of aromatic aldehydes and ketones exhibit geometrical isomerism of the *cis,trans*-type, except that the isomeric forms are designated *syn* and *anti*. Such an isomerism would not be possible if the three valence

bonds about a tercovalent nitrogen atom lay in a plane, or if there were free rotation about the carbon-to-nitrogen double bond.

Benzaldehyde, with hydroxylamine, forms an oxime that melts at 35°, called the *alpha*-form. This with hydrogen chloride forms a hydrochloride. When the reaction is carried out with cooling, the salt so obtained, m.p. 103 to 105°, regenerates the α-oxime on the addition of base, but if there is no cooling the salt, m.p. 108° (when anhydrous), is obtained. This, when decomposed with sodium carbonate, gives an isomeric, β-oxime melting at 128 to 130°. The α-salt changes to the β-salt on recrystallization. The β-oxime is rapidly converted into the α-isomer by heating or by the addition of a trace of acid. An important difference between the two forms is the behavior of the respective acetate with a base. the α-acetate, m.p. 14 to 16°, regenerates the α-oxime, but the β-acetate, m.p. 55 to 56°, is converted into benzonitrile by the elimination of a molecule of acetic acid. Formerly it was believed that the β-isomer had the *syn*-structure, on the basis that acetic acid would be lost easier if the H and CH_3COO groups were on the same side of the double bond. However, much evidence has accumulated to show that a molecule of acetic acid is lost more easily when the two groups are in the *trans*-position. This is shown by the reactions of the β-isomer of 2-chloro-5-nitrobenzaldoxime, for which the *anti*-configuration is indicated by the formation of an isoxazole ring (Chap. 44) when the oxime is heated with a base. The oxime is transformed into 2-chloro-5-nitrobenzonitrile by the action of acetic anhydride.

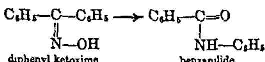


From this and other evidence α-benzaldoxime is regarded as the *syn*-isomer, and β-benzaldoxime as the *anti*-isomer. The formulas show the interrelations of α- and β-benzaldoximes.



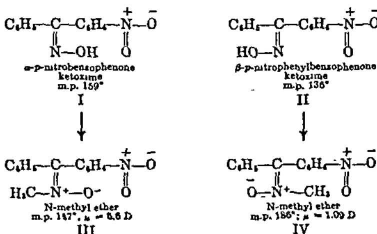
Many aromatic ketoximes exist in *syn*- and *anti*-forms. In these the two radicals attached to the ketone carbon atom are different. Ketoximes undergo an interesting rearrangement, the Beckmann rearrangement.

The Beckmann Rearrangement. Ketoximes, in the presence of a little phosphorus pentachloride or concentrated sulfuric acid, rearrange to N-substituted amides. Thus benzophenone oxime (diphenyl ketoxime) yields N-phenylbenzamide (benzanilide).

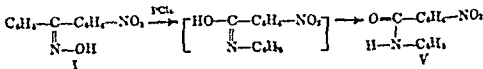


It is seen that a phenyl group migrates from carbon to nitrogen and an oxygen atom migrates in the reverse direction, from nitrogen to carbon.

In the case of unsymmetrical ketoximes, for example, *p*-nitrobenzophenone ketoxime, configurations were assigned originally on the assumption that in the Beckmann rearrangement exchange takes place between the hydroxyl group and the radical on the same side of the double bond. But this assumption led to inconsistencies in the case of the benzil diketoximes. Moreover, dipole measurements in some cases showed these assignments to be incorrect For example, there are two ketoximes of *p*-nitrobenzophenone, I and II, and from each of these, in addition to the O-ethyl ether, an N-methyl ether, III and IV, respectively, is formed by the action of dimethyl sulfate on the sodium salt of the ketoxime.



Since III has a higher electric dipole moment than IV, the two dipolar linkages ($\overset{+}{N}$—$\overset{-}{O}$) must reinforce each other in III and oppose each other in IV. Thus I is *syn-p*-nitrobenzophenone oxime, and II is *anti-p*-nitrobenzophenone oxime, where *syn* indicates that the hydroxyl and nitro groups are on the same side of the double bond, and *anti*, that they are on opposite sides. Since I is converted into *p*-nitrobenzanilide (the anilide of *p*-nitrobenzoic acid), V, by phosphorus pentachloride and II is converted exclusively into benz-*p*-nitroanilide (the *p*-nitranilide of benzoic acid), VI, it must be concluded that the hydroxyl group exchanges position with the radical in the *trans*-position.



$$\underset{\text{II}}{C_6H_5-\underset{\underset{HO-N}{\|}}{C}-C_6H_4-NO_2} \xrightarrow{PCl_5} \left[\begin{array}{c} C_6H_5-C-OH \\ \| \\ O_2N-C_6H_4-N \end{array}\right] \longrightarrow \underset{\text{VI}}{\begin{array}{c} C_6H_5-C=O \\ | \\ O_2N-C_6H_4-N-H \end{array}}$$

The intermediate compound is unstable and by migration of a proton goes over to the final stable amide.

Phenylhydrazones. There are many known examples of geometrical isomerism of phenylhydrazones. Acetaldehyde phenylhydrazone exists in two forms, *viz.*, α-isomer, m.p. 98°, and β-isomer, m.p. 56°. These form a continuous series of solid solutions but can be separated by distillation at reduced pressure, for the β-form is the more volatile. The α-form is converted completely into the β-form by a little acid; the reverse change is brought about, but only in part, by a trace of base. In the aromatic series many pairs of *syn*- and *anti*-isomers are known.

Individual Compounds. Many aromatic aldehydes and some ketones occur naturally, and may be constituents of essential oils (p. 507). They have characteristic odors or flavors, and these are largely responsible for the aromatic character of many natural products, for example, benzaldehyde in oil of bitter almonds, salicylaldehyde in oil of spiraea (from blossoms of the meadowsweet) and in other oils, anisaldehyde in cassia flowers and oil of anise, vanillin in the vanilla bean, and cinnamaldehyde in oil of cinnamon.

CHO (benzene ring) — benzaldehyde

CHO, OH (benzene ring) — salicylaldehyde

CHO, OCH_3 (benzene ring) — anisaldehyde

CHO, OCH_3, OH (benzene ring) — vanillin

CHO, O–CH_2–O (benzene ring) — piperonal

CH=CHCHO (benzene ring) — cinnamaldehyde

$COCH_3$ (benzene ring) — acetophenone

$CH_2CH_2COCH_3$, OCH_3, OH (benzene ring) — zingerone

CHO, CH_3O, $COCH_3$ (benzene ring) — 3-acetyl-6-methoxybenzaldehyde

Benzaldehyde, C_6H_5CHO. This was discovered by Martrés and Vogel in 1819. It and other benzoyl compounds were investigated by Liebig and Wöhler, 1832. They showed that the benzoyl radical remained intact in the transformation of a number of compounds, for example, benzoic acid, benzoyl chloride, and benzoic ester.

Benzaldehyde occurs in bitter almonds, and also to some extent in the kernels of the seeds of a number of related fruits, for example, plum, peach, and cherry, as the compound **amygdalin,** $C_{20}H_{27}NO_{11}$. This is a glycoside of mandelonitrile and the disaccharide, gentiobiose. Hydrolysis with hydrochloric acid gives benzaldehyde, hydrocyanic acid, and glucose (see p. 537). Benzaldehyde occurs in other plants. Benzaldehyde is manufactured by oxidation of toluene or hydrolysis of benzal chloride. It is used for the preparation of dyes, and finds application as a flavoring agent and also in the perfumery industry.

Salicylic Aldehyde, o-HOC$_6$H$_4$CHO. This is prepared by the Reimer-Tiemann reaction from phenol and chloroform (p. 499) and is separated *from the para-isomer* by steam distillation. Its greater volatility, like that of the nitrophenols, is ascribed to chelation, resulting from intramolecular hydrogen bonding. It is an intermediate in the manufacture of coumarin

TABLE 91 | **Some Aromatic Aldehydes and Ketones**

NAME	M.P. °C	B.P. °C	OCCURRENCE
Benzaldehyde	−26	178.1	bitter almond
p-Tolualdehyde		204–205	
Salicylaldehyde [a]	1.6	197	meadowsweet
p-Hydroxybenzaldehyde [b]	116		grass tree resin
o-Methoxybenzaldehyde	37	244	
Anisaldehyde	2.5	248	oils of anise, cassia, etc.
Vanillin [c]	81.5	285	vanilla bean
Piperonal	37	263	black locust flowers
Cinnamaldehyde	−7.5	253.5	oils of cinnamon and cassia
Acetophenone	20.5	202	oil of castoreum
Propiophenone	21	218	
Zingerone [d]	40–41		ginger root
3-Acetyl-6-methoxybenzaldehyde	144		brittle bush
Benzophenone	48.1	305.5	
Phenyl *p*-tolyl ketone	59(55)	326.5	
Benzil	95	346–348	
Benzoin	137	344	
Benzalacetone	42	260–262	
Dibenzalacetone	113	230 [e]	

Color with ferric chloride: [a] violet; [b] weak violet; [c] blue violet; [d] green. [e] At 20 mm.

Anisaldehyde, *p*-Methoxybenzaldehyde, *p*-CH$_3$OC$_6$H$_4$CHO. This may be prepared by the oxidation of anethole, *p*-CH$_3$OC$_6$H$_4$CH=CHCH$_3$ (p. 505).

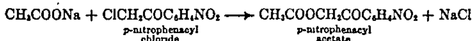
Vanillin, 1,3,4-C$_6$H$_3$CHO(OCH$_3$)OH. This is extracted from the vanilla bean by alcohol, yielding the ordinary extract of vanilla. Synthetic vanillin is called upon to help meet the needs for vanilla flavoring. One method is the Reimer-Tiemann synthesis from guaiacol (p. 506), another, oxidation of isoeugenol (p. 506). A more recent source is lignin, a constituent of wood. Vanillin is a much stronger acid than phenol (K_a = 4.8 × 10^{-8}).

Piperonal, Heliotropin, 3,4-Methylenedioxybenzaldehyde, 1,3,4-CHO—C$_6$H$_3$O$_2$CH$_2$. This is related to vanillin, except that both hydroxyl groups are in combination as a cyclic formal. It can be prepared by the oxidation of isosafrol (p. 506). Piperonal has a hyacinthlike odor and is used in perfumery.

Cinnamaldehyde, C$_6$H$_5$CH=CHCHO. This is best isolated from oil of cinnamon or cassia in the form of sodium bisulfite addition compound. Cinnamaldehyde can be reduced to β-phenylpropanal (hydrocinnamaldehyde) by saturation of the double bond, a change effected by hydrogenating with one mole of hydrogen under ordinary conditions with a nickel catalyst, and to cinnamyl alcohol by aluminum isopropoxide (p. 264) or lithium aluminum hydride (p. 133), reagents that do not re-

duce the double bond. It is reduced to 3-phenyl-1-propanol by complete reduction, as by electrolytic reduction with a mercury cathode or by hydrogenation at 2 to 3 atmospheres pressure with a platinum oxide catalyst. As in the case of acrylic aldehyde, one or two molecules of sodium bisulfite add (p. 288). Three different compounds are known in this case, two with one molecule of sodium bisulfite, one with two.

Acetophenone, Methyl Phenyl Ketone, $C_6H_5COCH_3$. This is named from the acetyl and phenyl groups, the ending -one indicating a ketone. Names of many other ketones are on a similar basis. The ketone is easily and best prepared by the Friedel-Crafts synthesis. Chlorination takes place rapidly on the side chain. The product, phenacyl chloride (ω-chloroacetophenone), also available from a Friedel-Crafts reaction of chloracetyl chloride with benzene, is a powerful lachrymator and was used as such in World War I. The compound is reactive. It and derivatives, for example, the nitro and p-phenyl compounds, are useful for making solid derivatives of acids, by reacting with the sodium salts



$$CH_3COONa + ClCH_2COC_6H_4NO_2 \longrightarrow CH_3COOCH_2COC_6H_4NO_2 + NaCl$$

p-nitrophenacyl chloride; p-nitrophenacyl acetate

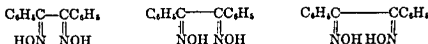
Benzalacetone, Benzylidene Acetone, $C_6H_5CH{=}CHCOCH_3$, and Dibenzalacetone, $C_6H_5CH{=}CHCOCH{=}CHC_6H_5$. These can be obtained by a condensation reaction between benzaldehyde and acetone (p. 517). The dibenzal compound is yellow. The reaction sometimes is used as a test for benzaldehyde

Zingerone, 3-Methoxy-4-hydroxybenzylacetone, 4-(3-Methoxy-4-hydroxyphenyl)-2-butanone. This is found in the root of the ginger plant (*Zingiber officinale*). It has a biting taste. It can be synthesized by the condensation of vanillin with acetone (as described above), followed by reduction of the resulting 3-methoxy-4-hydroxybenzalacetone.

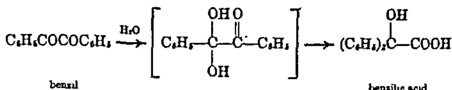
3-Acetyl-6-methoxybenzaldehyde, 1,3,6-CHO—$C_6H_3(COCH_3)OCH_3$. This occurs in the leaves of a desert shrub, *Encelia farinosa*, commonly called brittle bush, sometimes incense bush. The chemical is a growth inhibitor and is believed to be responsible for the sparsity of growth of annuals in the vicinity of *Encelia*.

Benzoin, $C_6H_5CHOHCOC_6H_5$. This is formed from benzaldehyde in the benzoin condensation (p. 518). Like aliphatic hydroxyketones, this is a good reducing agent, reducing ammoniacal silver and hot Fehling solutions. When heated with concentrated nitric acid it is oxidized to benzil. By the action of sodium amalgam in water or aqueous alcohol, benzoin is converted to hydrobenzoin, α,α′-diphenylethyleneglycol, $C_6H_5CHOHCHOHC_6H_5$.

Benzil, $C_6H_5COCOC_6H_5$, and Benzilic Acid, $(C_6H_5)_2C(OH)COOH$. Benzil is the simplest purely aromatic diketone and is obtained from benzoin by oxidation. One reagent often used is copper sulfate dissolved in pyridine. Benzil, like biacetyl (p. 287), is yellow. It forms three isomeric diketoximes. These are called *anti-*, *amphi-* and *syn*-benzildioxime, respectively.



Benzil undergoes an interesting change, called the benzilic acid rearrangement, when heated with water or, more rapidly, with aqueous (or alcoholic) base.



The change involves a shift of the phenyl group in one direction and that of the hydroxyl group in the opposite, recalling rearrangement of ketoximes (p. 520). The base is believed to promote the reaction by removing a proton from the migrating hydroxyl group.

PROBLEMS

1. *Starting with benzene, toluene, or p-xylene as the only aromatic compound, show how* the following may be prepared, reasonably free of isomeric forms.

a) o-nitrobenzyl alcohol
b) m-nitrobenzyl alcohol
c) p-nitrobenzyl alcohol
d) o-bromobenzyl alcohol
e) m-bromobenzyl alcohol
f) p-bromobenzyl alcohol
g) o-fluorobenzyl alcohol
h) m-fluorobenzyl alcohol
i) p-fluorobenzyl alcohol
j) p-methylbenzyl alcohol

2. Ditto:

a) p-methylbenzaldehyde
b) salicylaldehyde
c) anisaldehyde
d) vanillin
e) piperonal
f) cinnamaldehyde
g) p-methylcinnamaldehyde
h) p-ethoxycinnamaldehyde
i) 3-p-methylphenyl-1-propanol
j) zingerone

3. *Starting with benzene, toluene, or p-xylene as the only aromatic compound, show how* the following, reasonably free of isomeric forms, would be expected to be synthesized by making use of the Reimer-Tiemann reaction:

a) 2-hydroxy-5-fluorobenzaldehyde
b) 2-hydroxy-5-methylbenzaldehyde
c) o-methoxybenzoic acid
d) 3-bromo-4-hydroxybenzaldehyde
e) 2-hydroxy-5-bromobenzaldehyde
f) 3-methyl-4-hydroxybenzaldehyde
g) 2-hydroxy-3-bromo-5-methylbenzaldehyde
h) 3-nitro-4-hydroxybenzaldehyde
i) p-ethoxybenzoic acid
j) 6-hydroxy-2,5-dimethylbenzaldehyde
k) 2-hydroxy-5-chlorobenzaldoxime
l) ethyl 2-hydroxy-5-fluorobenzoate
m) p,p′,p″-trihydroxytriphenylmethane
n) 4-hydroxy-2,5-dimethylbenzaldehyde
o) 3-methyl-4-hydroxymandelic acid
p) 3-nitro-6-hydroxy-2,5-dimethylbenzaldehyde
q) 6-acetoxy-3-methylcinnamic acid
r) 4,4′-dimethoxybenzoin

4. Starting with 1-butanol as the aliphatic component, show steps and reagents for a practical synthesis of:

a) *n*-butyrophenone
b) *n*-valerophenone
c) *n*-butyl phenyl ether
d) *n*-butylphenylcarbinol
e) *n*-propyl *p*-hydroxyphenyl ketone
f) *n*-butyl *p*-hydroxyphenyl ketone
g) 2,4-dihydroxypropiophenone
h) 2,4-dihydroxybutyrophenone
i) *p*-hydroxy-*n*-butylbenzene
j) *p*-hydroxy-*n*-amylbenzene
k) 2,4-dihydroxy-*n*-butylbenzene
l) 2,4-dihydroxy-*n*-amylbenzene
m) *p*-*n*-butylbenzaldehyde
n) *p*-*n*-amylbenzaldehyde
o) *p*-*n*-butylbenzyl alcohol
p) *p*-*n*-amylbenzyl alcohol

5. Describe a convenient chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) benzyl alcohol and *o*-cresol
b) benzyl alcohol and phenetole
c) benzyl alcohol and *p*-xylene
d) benzyl alcohol and dibenzyl ether
e) benzyl alcohol and benzaldehyde
f) benzaldehyde and salicylaldehyde
g) benzaldehyde and anisaldehyde
h) benzaldehyde and vanillin
i) benzaldehyde and piperonal
j) benzaldehyde and cinnamaldehyde
k) benzaldehyde and acetophenone
l) benzaldehyde and benzoin
m) benzaldehyde and benzil
n) benzaldehyde and resorcinol
o) benzaldehyde and hydroquinone
p) benzaldehyde and propiophenone
q) acetophenone and methyl cyclohexyl ketone
r) acetophenone and ethylbenzene
s) acetophenone and *p*-tolualdehyde
t) acetophenone and phenacyl chloride

6. Compound *A*, $C_{11}H_{12}O$, is a liquid, only very slightly soluble in water or in dilute aqueous acid or base. Its aqueous solution immediately reduces aqueous permanganate, but not ammoniacal silver nitrate. With hydroxylamine *A* forms compound *B*, $C_{11}H_{13}ON$. This acts similarly towards permanganate. In ethyl acetate solution *A* gives a reaction product with ozone, and this in turn, when added to water and zinc dust, yields benzaldehyde, among other products. What deductions can be drawn from these statements? Show how they lead to a structure for *A*.

7. Liquid compound *A*, $C_9H_{10}O_2$, insoluble in water or in dilute aqueous acid or base, gives a solid, *B*, when added to a hot solution of 2,4-dinitrophenylhydrazine in glacial acetic acid. When *A* is heated for some time with aqueous sodium hydroxide, there is a decrease in volume of the organic phase, which becomes compound *C*, $C_8H_{12}O_2$. Addition of sulfuric acid to the aqueous phase to *p*H 3 causes solid *D*, $C_9H_{10}O_3$, to separate. This dissolves in concentrated hydriodic acid. Slow distillation of the solution gives a two-phase distillate, the lighter miscible with water, the lower immiscible with water and distilling, when anhydrous, at 71°.

What deductions can be drawn from these statements? Show how they lead to a structure for *A*. Indicate the reaction steps. Is more than one structure for *A* possible?

CHAPTER 35

Aromatic Acids

Quite a number of aromatic acids occur naturally. In the essential oils, resins, and balsams obtained from various plants are found such acids as benzoic, salicylic, and cinnamic. In the widely distributed groups of tannins is found gallic acid, a trihydroxybenzoic acid. In the protein of plants and animals are found the amino acids, phenylalanine and tyrosine. On the whole, the aromatic acids constitute an important class of organic compounds. The general methods of preparation and general reactions need be mentioned but briefly, since they resemble those of aliphatic acids.

Preparation. Aromatic acids may be prepared by the methods applicable to aliphatic acids (Chap. 12), for example, oxidation of aldehydes or primary alcohols, carbonation of Grignard reagents and hydrolysis of esters, amides, or nitriles. The last can be obtained from the appropriate sulfonic acid by alkali fusion (p. 457) or from the corresponding amine, through the diazo reaction (p. 486). Other methods, not applicable to aliphatic acids are: oxidation of side chains, carbonation of phenols (for hydroxy acids), and condensation of aldehydes with anhydrides (the Perkin synthesis of unsaturated acids, p. 518).

Vigorous oxidation of a benzene homolog, as for example with chromic acid mixture, leads to the formation of an acid having the carboxyl group attached to the ring. The rest of the side chain is lost during the oxidation. Sometimes acetophenone is an intermediate product as, for example, from ethylbenzene and *sec*-butylbenzene. Hydroxy acids are obtained by carbonation of phenols, as in the Kolbe synthesis of salicylic acid (p. 500). Unsaturated acids are prepared by the Perkin reaction (p. 518), and these when reduced yield acids having the carboxyl group on a saturated side chain.

Properties. Aromatic acids are solids of medium to high melting points, fairly high boiling points (250° and above), low to medium solubility in water (medium if hydroxyl groups are present), moderate to good solubility in alcohol and ether. They dissolve in dilute aqueous sodium carbonate or hydroxide and are precipitated from such solutions on the addition of a strong acid. They are usually purified by crystallization.

ACIDS HAVING THE CARBOXYL GROUP ON THE BENZENE RING

General Chemical Properties. These acids, like aliphatic carboxylic acids, react ionically in aqueous solution with aqueous bases. The benzene ring enhances acid strengths, for benzoic acid ($K_a = 6.6 \times 10^{-5}$) is a stronger acid than acetic acid (1.8×10^{-5}). Under anhydrous conditions aromatic acids undergo other typical reactions, for example, formation of esters, acyl halides, anhydrides, and amides. In general, these are slower than similar reactions of aliphatic acids. For example, acetyl chloride reacts completely in a few seconds at 0° with anhydrous ethyl alcohol, whereas benzoyl chloride requires about four hours for complete reaction. The carboxyl group of an aromatic acid is more easily reduced than that of an aliphatic acid. Electrolytic reduction of benzoic acid in alcohol–sulfuric acid solution with lead electrodes gives benzaldehyde, and reduction by heating with water and sodium amalgam, while keeping the mixture acid by continual addition of hydrochloric acid, gives benzyl alcohol along with other products.

The benzene ring undergoes substitution and reduction as its principal reactions. In substitutions, such as halogenation, nitration, and sulfonation, the carboxyl group is *meta*-directive (p. 436), and thus substitution is more difficult than in the case of benzene. On the other hand, the ring is more easily reduced. Benzoic acid is converted to cyclohexanecarboxylic acid by hydrogen in ether with a platinum black catalyst at ordinary temperature, by hydrogen with a nickel catalyst when heated, or by the action of metallic sodium in boiling amyl alcohol. Phthalic acids (benzenedicarboxylic acids) are still more easily reduced and undergo stepwise reduction with sodium amalgam and water, yielding dicarboxylic acid derivatives of cyclohexadiene and cyclohexene.

Benzoic Acid, C_6H_5COOH. This was obtained at the beginning of the seventeenth century from gum benzoin by sublimation. It was investigated by Liebig and Wöhler, who showed its relationship to benzaldehyde in their classical paper published in 1832. The value of this research on the benzoyl compounds in its relation to the development of organic chemistry cannot be overestimated. They showed that the radical, benzoyl, C_6H_5CO, passes intact from compound to compound and is present in benzaldehyde, benzoic acid, benzoic ester, benzoyl chloride, and benzamide. Their results and those of Gay-Lussac on cyanogen (p. 386) laid the foundations for the development of organic chemical theory.

Benzoic acid is a colorless solid melting at 122.4° and boiling at 250.0°; it sublimes readily when heated and is volatile with steam. It can be recrystallized from water, in which it has the following solubilities: 0.34 g. at 25°, 5.56 g. at 100°. It is manufactured from toluene by direct oxidation or by chlorination to benzotrichloride, $C_6H_5CCl_3$, and hydrolysis of the latter (p. 454). The sodium salt has mild antiseptic properties and has been used as a preservative in foods. This practice is permitted by the Federal Government and by most state governments, provided the amount does not exceed 0.1 per cent and the label declares the presence of the preservative. Benzoic acid is used in medicine and in the preparation of certain dyes, for example, aniline blue.

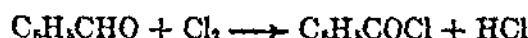
Derivatives of Benzoic Acid. Included here are the acyl chloride, some esters, the amide, and the peracid. The methods of their formation are applicable to other similar compounds.

Benzoyl Chloride, C_6H_5COCl. This is a colorless liquid boiling at 194°. A convenient laboratory preparation is the reaction of benzoic acid with phosphorus pentachloride.



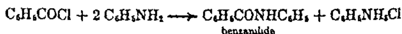
$$C_6H_5COOH + PCl_5 \longrightarrow C_6H_5COCl + HCl + POCl_3$$

It is manufactured by the chlorination of benzaldehyde at elevated temperatures.

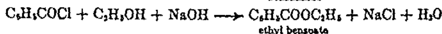


$$C_6H_5CHO + Cl_2 \longrightarrow C_6H_5COCl + HCl$$

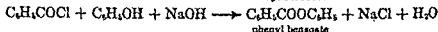
Benzoyl chloride has a disagreeable odor and is a strong lachrymator. It is much less reactive than acetyl chloride (p. 527). It is useful in the benzoylation of amines, alcohols, and phenols. The hydroxy compounds are benzoylated in the presence of dilute aqueous sodium hydroxide, which markedly accelerates the reaction.



$$C_6H_5COCl + 2\,C_6H_5NH_2 \longrightarrow \underset{\text{benzanilide}}{C_6H_5CONHC_6H_5} + C_6H_5NH_3Cl$$



$$C_6H_5COCl + C_2H_5OH + NaOH \longrightarrow \underset{\text{ethyl benzoate}}{C_6H_5COOC_2H_5} + NaCl + H_2O$$



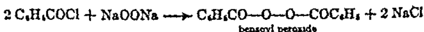
$$C_6H_5COCl + C_6H_5OH + NaOH \longrightarrow \underset{\text{phenyl benzoate}}{C_6H_5COOC_6H_5} + NaCl + H_2O$$

Benzoylation of hydroxy compounds in the presence of aqueous sodium hydroxide is called the Schotten-Baumann reaction. The benzoylated compounds are oftentimes crystalline solids and useful for purposes of identification.

Methyl Benzoate, $C_6H_5COOCH_3$, and Ethyl Benzoate, $C_6H_5COOC_2H_5$. These are usually prepared by several hours heating of the anhydrous alcohol containing benzoic acid and a catalyst, usually hydrogen chloride or hydrogen sulfate; b p. 199° and 212°, respectively. The Schotten-Baumann reaction is convenient for the preparation of small amounts, because of the speed. The methyl ester occurs naturally, for example, in tuberose oil.

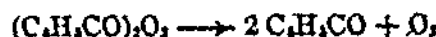
Benzamide, $C_6H_5CONH_2$. This forms when aqueous ammonia is added to benzoyl chloride. The ammonolysis reaction is aided by addition of an organic solvent, for example, acetone. The amide is a colorless solid melting at 130° and has a low solubility in cold water. The K_a lies between 10^{-14} and 10^{-15}.

Benzoyl Peroxide, $(C_6H_5CO)_2O_2$, and Perbenzoic Acid (Benzoylhydroperoxide, Peroxybenzoic Acid), $C_6H_5CO_2OH$. The peroxide is obtained by the action of benzoyl chloride on sodium peroxide.



$$2\,C_6H_5COCl + NaOONa \longrightarrow \underset{\text{benzoyl peroxide}}{C_6H_5CO{-}O{-}O{-}COC_6H_5} + 2\,NaCl$$

Benzoyl peroxide is relatively stable and melts at 106 to 108°. It is a strong oxidizing agent. It decomposes when heated; the decomposition proceeds via a free radical mechanism.



$$(C_6H_5CO)_2O_2 \longrightarrow 2\,C_6H_5CO + O_2$$

The free benzoyl radicals promote further decomposition or they may react with some other organic compound, if one is present. One of the most important uses of benzoyl peroxide is the initiation of polymerization. Thus, in the case of methyl methacry-

late, the benzoyl radical first adds to the unsaturated ester, forming a free radical, that in turn can react rapidly with another molecule, and so on, to form the polymer.

$$C_6H_5\overset{O}{\overset{\|}{C}}\cdot + CH_2{=}\underset{CH_3}{\overset{CO_2Me}{C}} \longrightarrow C_6H_5COCH_2{-}\underset{CH_3}{\overset{CO_2Me}{C}}\cdot$$

$$C_6H_5COCH_2{-}\underset{CH_3}{\overset{CO_2Me}{C}}\cdot + CH_2{=}\underset{CH_3}{\overset{CO_2Me}{C}} \longrightarrow C_6H_5COCH_2{-}\underset{CH_3}{\overset{CO_2Me}{C}}{-}CH_2{-}\underset{CH_3}{\overset{CO_2Me}{C}}\cdot \longrightarrow \text{polymer}$$

Other polymerizations can be induced similarly, for example, that of butadiene.

Benzoyl peroxide reacts with sodium ethoxide, forming ethyl benzoate and sodium benzoylperoxide (sodium perbenzoate, sodium peroxybenzoate).

$$(C_6H_5CO)_2O_2 + EtONa \longrightarrow C_6H_5CO_2Et + C_6H_5CO_2ONa$$

Addition of acid to the sodium salt gives benzoylhydroperoxide (peroxybenzoic acid, perbenzoic acid). It is much less stable than benzoyl peroxide and is a stronger oxidizing agent. It is the first compound formed in the oxidation of benzaldehyde by oxygen (p. 516). Benzoylhydroperoxide forms epoxy compounds (olefin oxides) with compounds having an olefinic double bond

$$\underset{\text{2-butene}}{CH_3CH{=}CH\cdot CH_3} + C_6H_5CO_2OH \longrightarrow \underset{\text{2,3-epoxybutane}}{CH_3\overset{\ulcorner O \urcorner}{CH{-}CH}CH_3} + C_6H_5COOH$$

Phthalic Acids, $C_6H_4(COOH)_2$. The *ortho*-isomer of benzene dicarboxylic acid is called **phthalic** acid, the *meta*-isomer, **isophthalic**, and the *para*-isomer, **terephthalic** acid. Of these, phthalic acid is by far the most important. It was first obtained in 1836 by the oxidation of naphthalene tetrachloride (1,2,3,4) with nitric acid (hence the name). *Phthalic acid can be obtained from o-xylene, isophthalic acid from* *m*-xylene, and terephthalic acid from *p*-xylene, by oxidation with nitric acid or permanganate. Chromic acid mixture has the disadvantage that it tends to destroy the ring when there is an *ortho*-substituent; *o*-xylene suffers complete oxidation.

TABLE 92 | Some Aromatic Di- and Polycarboxylic Acids and Derivatives

NAME	M.P. °C	B.P. °C	SOLY. IN H_2O, 25° G./100 G.	K_1	K_2
Phthalic Acid	231 [a]	dec.	0.70	1.2×10^{-3}	3×10^{-6}
Isophthalic Acid	348.5	subl.	0.013	2.9×10^{-4}	2.7×10^{-5}
Terephthalic Acid	subl.		0.0016	1.5×10^{-4}	
Mellitic Acid	288	dec.	v. sol.	3×10^{-2}	6×10^{-3}
Phthalic Anhydride	131.2	284.5	reacts		
Phthalimide	238	subl.	0.036	5×10^{-9}	
Phthalonic Acid [b]	146 [c]	dec.	115 [d]	3×10^{-2}	

[a] Rapid heating. [b] Crystallizes with 2 H_2O. Anhydrous. [d] At 15°

Derivatives of Benzoic Acid. Included here are the acyl chloride, some esters, the amide, and the peracid. The methods of their formation are applicable to other similar compounds.

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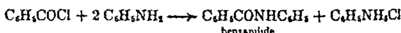
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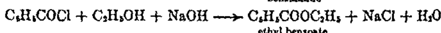


$$C_6H_5CHO + Cl_2 \longrightarrow C_6H_5COCl + HCl$$

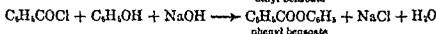
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$$C_6H_5COCl + C_2H_5OH + NaOH \longrightarrow \underset{\text{ethyl benzoate}}{C_6H_5COOC_2H_5} + NaCl + H_2O$$



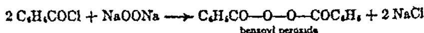
$$C_6H_5COCl + C_6H_5OH + NaOH \longrightarrow \underset{\text{phenyl benzoate}}{C_6H_5COOC_6H_5} + NaCl + H_2O$$

Benzoylation of hydroxy compounds in the presence of aqueous sodium hydroxide is called the Schotten-Baumann reaction. The benzoylated compounds are oftentimes crystalline solids and useful for purposes of identification.

Methyl Benzoate, $C_6H_5COOCH_3$, and Ethyl Benzoate, $C_6H_5COOC_2H_5$. These are usually prepared by several hours heating of the anhydrous alcohol containing benzoic acid and a catalyst, usually hydrogen chloride or hydrogen sulfate; b.p. 199° and 212°, respectively. The Schotten-Baumann reaction is convenient for the preparation of small amounts, because of the speed. The methyl ester occurs naturally, for example, in tuberose oil.

Benzamide, $C_6H_5CONH_2$. This forms when aqueous ammonia is added to benzoyl chloride. The ammonolysis reaction is aided by addition of an organic solvent, for example, acetone. The amide is a colorless solid melting at 130° and has a low solubility in cold water. The K_a lies between 10^{-14} and 10^{-15}.

Benzoyl Peroxide, $(C_6H_5CO)_2O_2$, and Perbenzoic Acid (Benzoylhydroperoxide, Peroxybenzoic Acid), $C_6H_5CO_2OH$. The peroxide is obtained by the action of benzoyl chloride on sodium peroxide.



$$2\,C_6H_5COCl + NaOONa \longrightarrow \underset{\text{benzoyl peroxide}}{C_6H_5CO{-}O{-}O{-}COC_6H_5} + 2\,NaCl$$

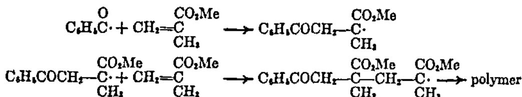
Benzoyl peroxide is relatively stable and melts at 106 to 108°. It is a strong oxidizing agent. It decomposes when heated; the decomposition proceeds via a free radical mechanism.



$$(C_6H_5CO)_2O_2 \longrightarrow 2\,C_6H_5CO + O_2$$

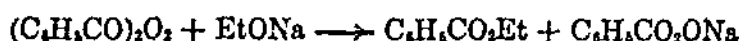
The free benzoyl radicals promote further decomposition or they may react with some other organic compound, if one is present. One of the most important uses of benzoyl peroxide is the initiation of polymerization. Thus, in the case of methyl methacry-

late, the benzoyl radical first adds to the unsaturated ester, forming a free radical, that in turn can react rapidly with another molecule, and so on, to form the polymer.

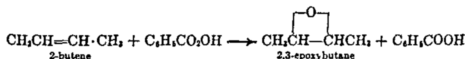


Other polymerizations can be induced similarly, for example, that of butadiene.

Benzoyl peroxide reacts with sodium ethoxide, forming ethyl benzoate and sodium benzoylperoxide (sodium perbenzoate, sodium peroxybenzoate).



Addition of acid to the sodium salt gives benzoylhydroperoxide (peroxybenzoic acid, perbenzoic acid). It is much less stable than benzoyl peroxide and is a stronger oxidizing agent. It is the first compound formed in the oxidation of benzaldehyde by oxygen (p. 516). Benzoylhydroperoxide forms epoxy compounds (olefin oxides) with compounds having an olefinic double bond.



Phthalic Acids, $C_6H_4(COOH)_2$. The *ortho*-isomer of benzene dicarboxylic acid is called **phthalic** acid, the *meta*-isomer, **isophthalic**, and the *para*-isomer, **terephthalic** acid. Of these, phthalic acid is by far the most important It was first obtained in 1836 by the oxidation of naphthalene tetrachloride (1,2,3,4) with nitric acid (hence the name). Phthalic acid can be obtained from *o*-xylene, isophthalic acid from *m*-xylene, and terephthalic acid from *p*-xylene, by oxidation with nitric acid or permanganate. Chromic acid mixture has the disadvantage that it tends to destroy the ring when there is an *ortho*-substituent; *o*-xylene suffers complete oxidation.

TABLE 92 | Some Aromatic Di- and Polycarboxylic Acids and Derivatives

NAME	M.P. °C	B.P. °C	SOLY. IN H_2O, 25° G./100 G.	K_1	K_2
Phthalic Acid	231 [a]	dec.	0.70	1.2×10^{-3}	3×10^{-6}
Isophthalic Acid	348 5	subl.	0.013	2.9×10^{-4}	$2 7 \times 10^{-5}$
Terephthalic Acid	subl.		0 0016	$1 5 \times 10^{-4}$	
Mellitic Acid	288	dec	v. sol.	3×10^{-3}	6×10^{-4}
Phthalic Anhydride	131.2	284.5	reacts		
Phthalimide	238	subl.	0.036	5×10^{-9}	
Phthalonic Acid [b]	146 [a]	dec.	115 [d]	3×10^{-2}	

[a] Rapid heating. [b] Crystallizes with 2 H_2O. Anhydrous. [d] At 15°

The three acids, by the action of sodium amalgam and water are reduced to dihydro and tetrahydro acids, by addition of hydrogen to the benzene ring. Phthalic acid has a variable melting point, with values ranging from 180 to 231°, the latter when the heating is rapid. Decomposition to the anhydride causes a lowering of the value. The three acids, like succinic acid, form high molecular weight esters when heated with glycols, *e g* , Dacron, a synthetic fiber, from terephthalic acid and ethylene glycol.

Phthalic Anhydride, 1,2-$C_6H_4(CO)_2O$. This is formed when phthalic acid is heated. It is an intermediate in the classical German process of making synthetic indigo, a process which developed industrially because of the discovery, in 1897, that naphthalene can be oxidized to phthalic anhydride by hot, fuming sulfuric acid containing mercuric sulfate, which acts as a catalyst. The sulfur dioxide formed in the reaction is reoxidized to sulfur trioxide by the contact process, the industrial development of which at that time assured the recovery of the sulfur dioxide and a resulting inexpensive sulfuric acid. The advent of World War I, with its consequent curtailment of imports into the United States, led to the gas phase oxidation process, developed by Weiss and Downs In this, naphthalene vapor and air are passed at temperatures of about 500° over vanadium pentoxide, which catalyzes the reaction. The product is phthalic anhydride, which hydrolyzes to phthalic acid when heated with water

The principal reactions of phthalic anhydride are ammonolysis, esterification with alcohols and glycols, and condensation with aromatic hydrocarbons, halogen compounds, and phenols

$$C_6H_4(CO)_2O + NH_3 \longrightarrow C_6H_4(CONH_2)(COOH) \xrightarrow{\text{heat}} C_6H_4(CO)_2NH$$

phthalic anhydride; phthalamidic acid; phthalimide

$$C_6H_4(CO)_2O + C_2H_5OH \longrightarrow C_6H_4(COOC_2H_5)(COOH)$$

ethyl acid phthalate

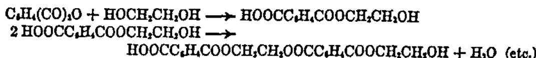
Half esters of phthalic acid are useful in identification of alcohols. Some of these esters are solids. Half esters can be converted into solid derivatives of satisfactory melting point by conversion first to sodium (or potassium) salts and reaction of these with a suitable reactive halogen compound, such as *p*-nitrophenacyl bromide.

$$C_2H_5OCO—C_6H_4—COOH + NaOH \longrightarrow C_2H_5OCO—C_6H_4—COONa + H_2O$$

$$C_2H_5OCO—C_6H_4—COONa + \underset{p\text{-nitrophenacyl bromide}}{BrCH_2CO—C_6H_4—NO_2} \longrightarrow \underset{\text{ethyl } p\text{-nitrophenacyl phthalate}}{C_2H_5OCO—C_6H_4—COOCH_2CO—C_6H_4—NO_2} + NaBr$$

Dimethyl phthalate is a repellent of mosquitos, flies, and other insects. Dibutyl phthalate is used extensively in plastics as a plasticizer.

Alkyd type resins are produced in a reaction of phthalic anhydride with glycols. Usually a little glycerol is added for cross-linkage.

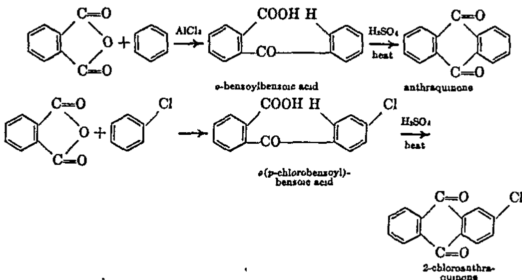


$$C_6H_4(CO)_2O + HOCH_2CH_2OH \longrightarrow HOOCC_6H_4COOCH_2CH_2OH$$

$$2\,HOOCC_6H_4COOCH_2CH_2OH \longrightarrow HOOCC_6H_4COOCH_2CH_2OOCC_6H_4COOCH_2CH_2OH + H_2O \text{ (etc.)}$$

Such resins are used as lacquers ("Glyptal").

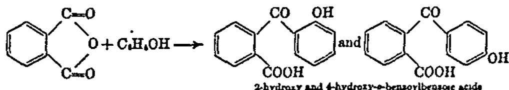
The condensation of phthalic anhydride with aromatic hydrocarbons and halogen compounds is a typical Friedel-Crafts reaction and is the first step in the synthesis of anthraquinone and numerous derivatives.



Heating with concentrated sulfuric or fuming sulfuric acid brings about ring closure. Many useful dyes are derived from anthraquinone (Chap. 46).

Phthalic anhydride is important industrially. Among the products made from it are phenolphthalein; dyes of the fluorescein, rhodamine, and anthraquinone types (Chap. 46); phthalimide and indigo (older process); and alkyd resins.

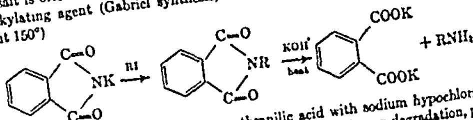
Phenols may condense with phthalic anhydride differently. With anhydrous aluminum chloride and acetylene tetrachloride as the solvent, reaction at around 120° gives the benzoylbenzoic acid reaction.



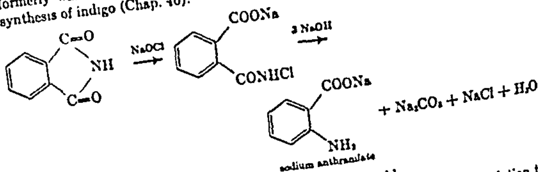
When heated at 120 to 140° with concentrated sulfuric acid, or about 180° with anhydrous zinc chloride, phenolphthalein is formed (p. 501). At a higher temperature with sulfuric acid the phenolphthalein slowly disappears and a mixture of 1-hydroxy and 2-hydroxyanthraquinone is obtained, resulting from ring closure of the two hydroxy compounds.

Phthalimide, $C_6H_4(CO)_2NH$. This may be obtained in a number of ways, for example, by heating acid ammonium phthalate or phthalamidic acid or, more conveniently, by passing a stream of ammonia gas over heated phthalic anhydride (p. 530). Phthalimide dissolves in cold dilute aqueous sodium hydroxide owing to its pronounced acidic character (Table 92). This is a result of the attachment of two

acyl radicals to the functional imide group. From the resulting aqueous solution phthalimide is precipitated on the addition of an acid. Potassium phthalimide is obtained by the action of an alcoholic solution of potassium hydroxide on phthalimide. This salt is often used for the preparation of pure primary amines by the action of an alkylating agent (Gabriel synthesis). Usually a high temperature is necessary (about 150°)



The degradation of phthalimide to anthranilic acid with sodium hypochlorite (in place of the more expensive sodium hypobromite in the Hofmann degradation, p. 374) formerly was an important industrial operation as one step in the earlier German synthesis of indigo (Chap. 46).



Addition of an acid to the sodium salt gives anthranilic acid.

Mellitic Acid, $C_6(COOH)_6$. This is of interest mainly because of its relation to graphite. It occurs in peat as the aluminum salt, $C_6(COO)_6Al_2 \cdot 18\ H_2O$, called honeystone. The acid can be isolated as an oxidation product of lignite, wood charcoal, or graphite when permanganate is the oxidizing agent. Its calcium salt when heated with lime yields benzene. The formation of mellitic acid from graphite has for decades been taken as evidence that the carbon atoms in graphite are arranged in six-membered rings. Analysis of graphite by X rays has definitely established such an arrangement. An unusual type of formula is that of a compound related to mellitic acid, namely $C_{12}O_9$, mellitic anhydride.

Substituted Benzoic Acids. The hydrogen atoms of the benzene nucleus may be replaced by a variety of substituents, as shown in Table 93. It is interesting to note the way in which the nature of the substituent and its position affect physical properties.

The melting point is raised by substituents other than methyl and is the highest for the *para*-isomer. The solubility of the *para*-isomer is the least of the three isomers. The nitro group has the greatest influence upon the ionization constant and causes a marked increase, as in the case of phenols; the amino group causes a decrease. When in the *ortho*-position all groups except amino bring about a marked increase in the ionization constant.

The Toluic Acids, $C_6H_4CH_3COOH$. These are obtained by the partial oxidation of the three xylenes and are converted into the three phthalic acids on oxidation. They resemble benzoic acid closely.

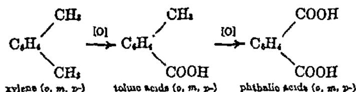


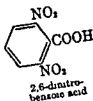
TABLE 93 | Some Aromatic Monocarboxylic Acids

NAME OF ACID	FORMULA	M.P. °C	B.P. °C	SOLY. IN H_2O AT 25° G./100 G.	$K_a \times 10^5$ 25°
Benzoic	C_6H_5COOH	122.4	250	0.34	6.3
o-Chlorobenzoic	ClC_6H_4COOH	140.6		0.225^{26}	132
m-Chlorobenzoic	ClC_6H_4COOH	154.25		0.045^{26}	15.5
p-Chlorobenzoic	ClC_6H_4COOH	241.5		0.0093^{26}	9.3
o-Bromobenzoic	BrC_6H_4COOH	148		0.185	145
m-Bromobenzoic	BrC_6H_4COOH	156		0.0402	13.7
p-Bromobenzoic	BrC_6H_4COOH	254.5		0.0056	6.6
o-Nitrobenzoic	$NO_2C_6H_4COOH$	146.8		0.75	656
m-Nitrobenzoic	$NO_2C_6H_4COOH$	141		0.344	34.5
p-Nitrobenzoic	$NO_2C_6H_4COOH$	242		0.028	40
o-Aminobenzoic [a]	$NH_2C_6H_4COOH$	146		0.52	1.0
m-Aminobenzoic [a]	$NH_2C_6H_4COOH$	179		0.77	1.6
p-Aminobenzoic [a]	$NH_2C_6H_4COOH$	187		0.31 [b]	1.2
o-Hydroxybenzoic	HOC_6H_4COOH	159		0.22	105
m-Hydroxybenzoic	HOC_6H_4COOH	201		1.08	8.3
p-Hydroxybenzoic	HOC_6H_4COOH	213		0.65	2.9
o-Toluic	$CH_3C_6H_4COOH$	105.5	259	0.1182	12.3
m-Toluic	$CH_3C_6H_4COOH$	111.7	263	0.098	5.4
p-Toluic	$CH_3C_6H_4COOH$	179.6	275	0.0345	4.2
α-Toluic	$C_6H_5CH_2COOH$	78	266.5		4.9
DL-Mandelic	$C_6H_5CH(OH)COOH$	120.5		22	43
Cinnamic-cis	$C_6H_5CH{=}CHCOOH$	*68* [c]		*0.84*	*13.2*
Cinnamic-*trans*	$C_6H_5CH{=}CHCOOH$	136.8	300	0.049	3.65

[a] $K_b \times 10^{12}$ (25°) *o*, 1.4; *m*, 12; *p*, 2.3. [b] At 14°. [c] Two allotropic forms, m.p. 58° and 42°.

Nitrobenzoic Acids. The *ortho-* and *para-*isomers are most conveniently obtained by the oxidation of the corresponding nitrotoluenes with alkaline permanganate, the *meta-* by the nitration of benzoic acid. Additional nitration of the latter yields 3,5-dinitrobenzoic acid. Since most esters of this acid are solids, it or its acid chloride is often employed in the identification of alcohols. 2,4,6-Trinitrobenzoic acid is obtained by the oxidation of 2,4,6-trinitrotoluene. On heating with water the acid loses carbon dioxide and is converted into 1,3,5-trinitrobenzene.

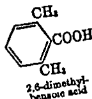
Steric Hindrance. Substituted benzoic acids containing substituents in the two *ortho*-positions are esterified at extremely low rates. Even the *ortho*-monosubstituted benzoic acids are esterified at rates much lower than the benzoic acid rate. The effect is not due to some special property of the substituent, because the different radicals methyl, chloro, and nitro in the following acids, produce much the same effect.



2,6-dinitrobenzoic acid



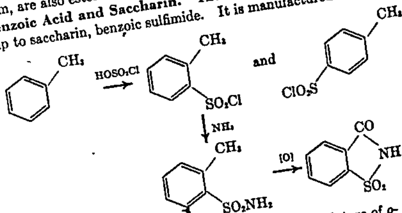
2,6-dichlorobenzoic acid



2,6-dimethylbenzoic acid

The esters of these acids can be made indirectly by the reaction of alkyl iodides upon the silver salts. Once made, the esters are very difficult to saponify. It would appear that the substituents surround the carboxyl group in the acids and the carbalkoxy group in the esters to such an extent that reaction is hindered. This is understandable on the basis that esterification and hydrolysis involve the formation of intermediate, unstable addition compounds (p. 226). Likewise, di-*ortho*-substituted acid chlorides and nitriles are very much more resistant to hydrolysis than benzoyl chloride and benzonitrile, respectively. It will be recalled that tertiary alcohols are esterified only slowly by aliphatic organic acids and that fatty acids, well branched at the *alpha* carbon atom, are also esterified slowly (p. 225).

Sulfobenzoic Acid and Saccharin. The *ortho*-acid is of interest because of its relationship to saccharin, benzoic sulfimide. It is manufactured from toluene.



Toluene is chlorosulfonated with chlorosulfonic acid to a mixture of *o*- and *p*-toluenesulfonyl chlorides. These are separated by a combination of distillation and crystallization (m.p. *ortho* 10.17°, *para* 66.67°). In the final step above, the *ortho*-compound spontaneously goes over into the cyclic form while the *para*-isomer remains as *p*-sulfamidobenzoic acid. Their separation is not easy since they are both slightly soluble in water and have ionization constants somewhat close to each other (saccharin = 3.9×10^{-3}; *p*-sulfamidobenzoic acid = 3.0×10^{-4}). This method is superior to the older method of sulfonation with fuming sulfuric acid, because, first, the proportion of *ortho*-isomer is greater, and second, the separation of the isomers is made at the sulfonyl chloride step.

Saccharin is remarkable in having an extraordinarily sweet taste, which has been estimated to be 550 times as sweet as that of cane sugar. It is used as a sweetening agent in place of sugar, especially by diabetics. Although only slightly soluble in water, it readily dissolves in aqueous sodium carbonate. It is marketed as the soluble sodium salt, which is called "soluble saccharin."

Aminobenzoic Acids, $NH_2C_6H_4COOH$. These may be obtained by the reduction of the corresponding nitrobenzoic acids with the usual reducing agents that do not attack the carboxyl group. The acids cannot be obtained by oxidizing the toluidines directly, since the latter are broken down by this treatment. However, if the

amino group is first protected by acetylation, then the methyl group can be oxidized by neutral permanganate. Removal of the acetyl group by heating with hydrochloric acid gives a salt of the corresponding aminobenzoic acid. The amino acids are amphoteric. The K_a and K_b values are given in Table 93. The basic constants are much smaller than the acidic constants. This is in distinct contrast to aliphatic amino acids, in which the basic strength is not greatly different from the acid strength (Chap. 40).

o-Aminobenzoic acid (anthranilic acid) was first obtained in the fusion of indigo (anil) with alkali. The acid occurs in jasmine and neroli (orange blossom) oils as the methyl ester; this is used as a constituent of perfumes and of grape flavors. The acid was for many years an intermediate in one of the industrial processes for manufacturing indigo; it is manufactured from phthalimide (p. 530) by treatment with sodium hypochlorite (Hofmann degradation, p. 374).

p-Aminobenzoic acid is one of the vitamins of the B complex. It is important in some of the chemical changes that take place in metabolism and in cell growth. It is a growth-promoting factor for the chick. The efficacy of sulfanilamide in depressing the growth of pathogenic bacteria is believed to be the result of *p*-aminobenzenesulfonamide replacing *p*-aminobenzoic acid.

Hydroxybenzoic Acids. The important acids are **salicylic acid, 1,2-$C_6H_4(COOH)OH$, protocatechuic acid, 1,3,4-$C_6H_3(COOH)(OH)_2$,** and **gallic acid, 1,3,4,5-$C_6H_2(COOH)(OH)_3$.** The first occurs in the leaves and stems of tulips and hyacinths, in the blossoms of the meadowsweet, and as the methyl ester in oil of wintergreen. Its name is derived from that of the willow (*Salix*); this contains a glucoside, salicin, that yields on hydrolysis glucose and saliginen (salicyl alcohol, *o*-hydroxybenzyl alcohol). When this is heated with solid potassium hydroxide, hydrogen is evolved and salicylic acid is precipitated on the addition of a strong acid. Protocatechuic acid is obtained by alkali fusion of many vegetable products, for example, resins, such as dragon's blood, gum benzoin, and Peru balsam, and colored substances, such as anthocyanins (Chap. 44). Gallic acid is widely distributed in plants and in combination with glucose is a component of tannins.

Salicylic acid can be obtained from anthranilic acid by the diazo reaction or from phenol by carbonation of sodium phenoxide (Kolbe synthesis, p. 500). When the latter reaction is carried out under pressure all of the phenol, instead of only half, is converted into salicylic acid. This is the usual synthetic process.

Salicylic acid is both an acid and a phenol. In aqueous solutions it readily forms a monosodium and a disodium salt with sodium hydroxide. The carboxyl group is esterified by an alcohol in the presence of a suitable catalyst, for example, anhydrous hydrogen chloride. The hydroxyl group may be esterified with an anhydride or acyl halide. In aqueous solution bromine water converts salicylic acid and also the isomeric *p*-hydroxybenzoic acid into tribromophenol, with expulsion of the carboxyl group.



$$HO—C_6H_4—COOH + 3\,Br_2 \longrightarrow HO—C_6H_2Br_3 + 3\,HBr + CO_2$$

Salicylic acid has strong antiseptic properties and, like benzoic acid, has been used in foods and beverages in the form of sodium salicylate, although its use is prohibited by pure food laws. In medicine it is employed as a remedy for rheumatism and also as an internal antiseptic; but when taken by mouth, its rapid absorption in the stomach may lead to some disorder. Certain derivatives which pass through the stomach unchanged and are slowly hydrolyzed to salicylic acid in the intestinal tract are of greater value, for example, aspirin and salol. They are of value also as antipyretics,

that is, temperature reducers. Industrially, salicylic acid is manufactured for conversion to these two substances and to its methyl ester, the essential constituent of oil of wintergreen.

Acetylsalicylic Acid, 1,2-$CH_3COOC_6H_4COOH$. This is made from sodium salicylate by the action of acetyl chloride or acetic anhydride alone, or from the acid and one of these alone, but preferably with a catalyst. Acetylsalicylic acid is a solid, soluble in water, 0.3 g. per 100 g., and melts at 137°. In the form of the water-soluble sodium salt, sodium acetylsalicylate, it is quite extensively sold as an analgesic and antipyretic. A common trade name is Aspirin.

Salol, 1,2-$HOC_6H_4COOC_6H_5$, the phenyl ester of salicylic acid, is made by heating salicylic acid, phenol, and phosphorus oxychloride at 120°:



$$3\,HOC_6H_4COOH + 3\,C_6H_5OH + POCl_3 \longrightarrow 3\,HOC_6H_4CO_2C_6H_5 + H_3PO_4 + 3\,HCl$$

It will be recalled that esters of phenol are made from the acid, phenol, and an acid chloride (p. 496). Salol is a powerful internal antiseptic, being converted into phenol and salicylic acid in the intestinal tract. It is a solid, insoluble in water, and melts at 42°.

Methyl Salicylate, 1,2-$HOC_6H_4COOCH_3$. This is the chief constituent of oil of wintergreen It is made by esterifying salicylic acid with methanol in the presence of anhydrous hydrogen chloride. It is an ingredient of many flavoring materials and of many remedies for sprains and bruises. Its value for the latter purpose is probably related to the property of being absorbed by the skin.

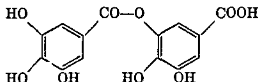
Gallic Acid, 1,3,4,5-$C_6H_2COOH(OH)_3$. This is an important constituent of the tannins, the astringent principle of many plants, and is formed from these on hydrolysis by boiling with dilute hydrochloric acid. This constitutes the usual method of preparation, since gallic acid cannot be easily and cheaply synthesized. Some gallic acid occurs free in gallnuts, the warty masses which grow on the branches of trees as the result of puncturing by insects. When heated to 220°, gallic acid loses carbon dioxide and is converted into pyrogallol, 1,2,3-$C_6H_3(OH)_3$. Like pyrogallol, it rapidly reduces silver and gold ions, and its alkaline solution readily absorbs oxygen from the air. The addition of ferric chloride throws down a bluish-black precipitate, which dissolves in excess of the reagent to form a green solution.

Tannins. These are substances of more or less indefinite composition which are widely distributed in nature in the bark of trees and in the leaves and roots of plants. Oak galls and the bark of oak, hemlock, and sumac are good sources of tannin. They possess the property of changing skin into leather, of precipitating glue, and of giving insoluble precipitates with alkaloids and with lead salts. Other characteristic properties of the tannins are the following: They are weak acids of high molecular weight, form colloidal solutions, have an astringent taste, reduce silver ion and Fehling's solution, precipitate proteins, and give a dark blue or green precipitate with ferric chloride. They are extensively used for the tanning of hides. For this purpose the bark containing the tannin and the hides are placed together in vats with water. The tannin, as it is slowly extracted from the bark by the water, is taken up by the hides, which slowly harden to leather. Chromium salts are also used for tanning purposes and are preferred by many tanners because the process can be carried out more rapidly than with tannin.

Chinese tannin, from Chinese gallnuts, is a mixture. It is composed of compounds that on hydrolysis give glucose and gallic acid, on the average nine gallic acid residues per glucose molecule. Glucose (p. 612) has only five hydroxyl groups and conse-

quently can hold only five molecules of gallic acid in combination. But two molecules of gallic acid can combine to form two different digallic acids (see below). It is one of these digallic acids which is in combination with glucose in Chinese tannin. The compound that has ten gallic acid molecules in combination can be regarded as a pentadigalloyl ester of glucose, $C_6H_7O(OH)_5$, $[(HO)_3C_6H_2COOC_6H_2(OH)_2COO]_5C_6H_7O$.

Digallic Acid, *m*-Galloylgallic Acid. This is often obtained as an intermediate product in the hydrolysis of some tannins. It is built up of two molecules of gallic acid and is synthesized in a complicated reaction that would be expected to yield the isomeric *p*-galloylgallic acid. The *meta*-isomer is the ester resulting from the esterification of the carboxyl group of one molecule of gallic acid by the *meta*-hydroxyl group of another.

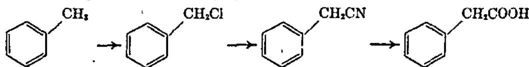


Emil Fischer synthesized pentadigalloylglucose and found that the synthetic product was remarkedly like Chinese tannin in many respects, such as bitter taste, characteristic tannin reactions, ability to tan hides, etc. However, there were certain differences which indicated that the synthetic was not identical with the natural product.

ACIDS HAVING THE CARBOXYL GROUP ON A SIDE CHAIN

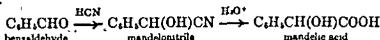
These acids are essentially aliphatic acids and are weaker than benzoic acid (Table 93). The most important of this group are those derived from β-phenylpropionic acid, for example, the unsaturated acid, cinnamic acid, and the *alpha*-amino acids, β-phenylalanine, tyrosine, and thyroxine (Chap. 40). β-Phenylpropionic acid itself is of minor importance.

Phenylacetic Acid, $C_6H_5CH_2COOH$. This is isomeric with the toluic acids, but differs in having the carboxyl group on the side chain. It is obtainable from toluene through benzyl chloride and benzyl cyanide.



It has been found that the yield of penicillin from the mold, *Penicillium notatum* is increased if phenylacetic acid is added to the mold culture. This is because phenylacetic acid is part of the structure of penicillin (Chap. 45).

Mandelic Acid, α-Hydroxyphenylacetic Acid, $C_6H_5CHOHCOOH$ (Ger. *Mandel*, almond). This is of interest in connection with asymmetric synthesis. The acid can be obtained from benzaldehyde, through benzaldehyde cyanohydrin (mandelonitrile).



$$\underset{\text{benzaldehyde}}{C_6H_5CHO} \xrightarrow{HCN} \underset{\text{mandelonitrile}}{C_6H_5CH(OH)CN} \xrightarrow{H_3O^+} \underset{\text{mandelic acid}}{C_6H_5CH(OH)COOH}$$

This synthetic acid is inactive (compare with lactonitrile, p. 302), and can be resolved into its *dextro-* and *levo-*forms with the alkaloid, cinchonine. An active acid is obtained by hydrolysis of *amygdalin*, a complex product occurring in bitter almonds; it is a combination of mandelonitrile and the disaccharide, gentiobiose (p. 636). Hydrolysis of amygdalin with hydrochloric acid gives glucose and (−)-mandelic acid.

One of the first asymmetric syntheses was accomplished (1904) by reduction of an ester of benzoylformic acid; the alcohol in combination with the acid was an optically active alcohol, *levo*-menthyl alcohol (Chap. 43). The mandelic acid recovered was levorotatory. This was due to a difference in the rates of formation of the *dextro*- and *levo*-forms of the acid part of the ester; that is, the optically active alcohol part of the ester caused one isomer to be formed more rapidly than the other.

$$\underset{(-)\text{-menthyl benzoylformate}}{C_6H_5\text{—CO—CO—}OC_{10}H_{19}} \xrightarrow{2[H]} \underset{\substack{(-)\text{-menthyl } (+)\text{-mandelate} \\ (-)\text{-menthyl } (-)\text{-mandelate}}}{C_6H_5\text{—CHOH—CO—}OC_{10}H_{19}} \xrightarrow{Ac_2O}$$

$$C_6H_5\text{—CHOAc—CO—}OC_{10}H_{19} \xrightarrow{H_2O} \underset{\substack{(+)\text{-mandelic acid} \\ (-)\text{-mandelic acid (in excess)}}}{C_6H_5\text{—C(H)(OH)—COOH}}$$

Another interesting type of asymmetric synthesis is the formation of mandelonitrile in the presence of an optically active base. It will be recalled that the cyanohydrin reaction is base catalyzed (p. 269). The most readily available optically active bases are alkaloids (Chap. 45). The first reactions of this type were carried out with (+)-quinidine, I, and (−)-quinine, II.

$$C_6H_5CHO + HCN \xrightarrow{\text{I}} C_6H_5\overset{*}{C}HOHCN \xrightarrow{H_3O^+} \underset{\substack{54.3\%\ dextro \\ 45.7\%\ levo}}{C_6H_5CHOHCOOH}$$

$$C_6H_5CHO + HCN \xrightarrow{\text{II}} C_6H_5\overset{*}{C}HOHCN \xrightarrow{H_3O^+} \underset{\substack{48.5\%\ dextro \\ 51.5\%\ levo}}{C_6H_5CHOHCOOH}$$

It is evident that the optically active base catalyzes the formation of one isomeric mandelonitrile faster than the other. Many asymmetric syntheses similar to those mentioned have been reported.

Finally, in the presence of **emulsin** (the enzyme present in bitter almonds that brings about the hydrolysis of amygdalin to glucose, benzaldehyde, and hydrogen cyanide) benzaldehyde and hydrogen cyanide react with each other to give mandelonitrile that is dextrorotatory. This is converted, by hydrolysis with hydrochloric acid, into mandelic acid that is levorotatory. This acid is not optically pure, but gives the pure (−)-acid after two crystallizations. The action of emulsion is characteristic of enzymes in general. These are naturally occurring, high molecular weight proteins (Chap. 41) that bring about chemical changes in living organisms. In a large number of cases the products of reactions possess optical activity and usually are optically pure isomers.

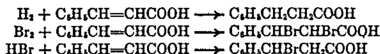
Cinnamic Acid, β-Phenylacrylic Acid, $C_6H_5CH{=}CHCOOH$. This is the most important of the unsaturated aromatic acids. It occurs in many natural products, such as oil of cinnamon, gum benzoin, storax, and the balsams of Peru and Tolu. It may be synthesized by the Perkin reaction, described in the preceding chapter (p. 518).

There should be two forms of cinnamic acid, *viz.*, a *cis*-acid and a *trans*-acid.

$$\underset{\textit{cis}\text{-cinnamic acid}}{\begin{array}{c}H\text{—C—}C_6H_5\\ \|\\ H\text{—C—COOH}\end{array}} \qquad \underset{\textit{trans}\text{-cinnamic acid}}{\begin{array}{c}C_6H_5\text{—C—H}\\ \|\\ H\text{—C—COOH}\end{array}}$$

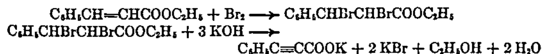
Actually, four forms are known, melting respectively at 42°, 58°, 68° (allocinnamic acid), and 134°. For many years chemists were at a loss to account for these. It is now known that the ordinary form, 134°, has the *trans*-configuration, and the other three are allotropic modifications, all having the *cis*-configuration The fused *cis*-acid from any one of these three solids can be converted into any one of them on addition of some of the respective solid phase. The forms melting at 42° and 58° are less stable. The *cis*-acid is obtained by the hydrogenation of phenylpropiolic acid with platinum as the catalyst.

Cinnamic acid shows the usual reactions of an unsaturated acid. It is reduced to hydrocinnamic by hydrogenation or by means of sodium amalgam and water. It slowly adds bromine, yielding α,β-dibromo-β-phenylpropionic acid, and hydrogen bromide (fuming hydrobromic acid), yielding β-bromo-β-phenylpropionic acid.



$$H_2 + C_6H_5CH{=}CHCOOH \longrightarrow C_6H_5CH_2CH_2COOH$$
$$Br_2 + C_6H_5CH{=}CHCOOH \longrightarrow C_6H_5CHBrCHBrCOOH$$
$$HBr + C_6H_5CH{=}CHCOOH \longrightarrow C_6H_5CHBrCH_2COOH$$

Phenylpropiolic Acid, $C_6H_5C{\equiv}CCOOH$. This is the simplest triply bonded aromatic acid. Its salt may be prepared from ethyl cinnamate.



$$C_6H_5CH{=}CHCOOC_2H_5 + Br_2 \longrightarrow C_6H_5CHBrCHBrCOOC_2H_5$$
$$C_6H_5CHBrCHBrCOOC_2H_5 + 3\,KOH \longrightarrow C_6H_5C{\equiv}CCOOK + 2\,KBr + C_2H_5OH + 2\,H_2O$$

Reduction of phenylpropiolic acid yields two products. By the use of zinc and dilute acetic acid, *trans*-cinnamic acid is formed, and with hydrogen in the presence of platinum, the *cis*-acid is obtained. It will be recalled that alkynes on reduction with sodium in liquid ammonia yield *trans*-olefins, and on hydrogenation with a metallic catalyst, *cis*-olefins. The formation of the *trans*-isomer is the normal type of addition (p. 83).

PROBLEMS

1. Outline a practical laboratory method (reagents and conditions) for obtaining *p*-toluic acid, reasonably free of isomers, from toluene by making use of one, but not more than one, of the following synthetic methods:

a) Wurtz-Fittig
b) Friedel-Crafts
c) Gattermann
d) Grignard
e) sulfonation
f) diazotization

2. Write equations, including actual reagents, for reactions involved in obtaining the following, reasonably pure, from toluene, and state how purification from any isomeric forms is accomplished:

a) *o*-sulfobenzoic acid
b) *m*-sulfobenzoic acid
c) *p*-sulfobenzoic acid
d) *o*-toluic acid
e) *m*-toluic acid
f) *p*-aminobenzoic acid
g) *o*-hydroxybenzoic acid
h) *m*-hydroxybenzoic acid
i) *p*-hydroxybenzoic acid
j) methyl *o*-hydroxybenzoate
k) ethyl *m*-diethylaminobenzoate
l) ethyl *p*-ethoxybenzoate
m) *o*-aminobenzamide
n) *m*-chlorobenzoyl chloride
o) *p*-iodobenzoic acid
p) *m*-fluorobenzamide

q) isopropyl *o*-fluorobenzoate
r) *o*-chloro-N,N-dimethylbenzamide
s) ethyl *p*-hydroxybenzoate
t) *p*-thiolbenzoic acid
u) phthalimide
v) phenyl cyanide
w) aniline
x) β-phenylpropionic acid
y) phenylpropiolic acid
z) *m*-nitropropiolic acid

3. Ditto.

a) benzenesulfonamide-*p*-carboxylic acid
b) N-chlorobenzenesulfonamide-*m*-carboxylic acid
c) 2-bromo-4-aminobenzoic acid
d) 2-sulfo-4-acetamidobenzoic acid
e) phthalic acid
f) isophthalic acid
g) terephthalic acid
h) 2-acetamido-5-carboxybenzenesulfonamide
i) 3-bromo-4-acetamidobenzoic acid
j) 3-amino-4-acetamidobenzoic acid
k) 2-chloro-4-methylbenzoic acid
l) 3-nitro-4-bromobenzoic acid
m) 3-methyl-4-hydroxy-2′-carboxyazobenzene
n) 2-nitro-4-amino-3,2′-dicarboxyazobenzene
o) 4-amino-5-fluoro-4′-carboxy-2-methylazobenzene
p) 3-iodo-4′-hydroxy-4-methyl-3′-carboxyazobenzene
q) *o*-toluylhydroperoxide
r) *p*-toluylhydroperoxide

4. Outline a practical synthesis of the following from benzene, toluene, or benzaldehyde by making use of the Perkin synthesis:

a) *o*-methoxycinnamic acid
b) α-methyl-β-phenylacrylic acid
c) *m*-ethoxycinnamic acid
d) *p*-methoxycinnamic acid
e) *m*-fluorocinnamic acid
f) β-*p*-dimethylaminophenylpropionic acid
g) β-bromo-β-*p*-tolylpropionic acid
h) α-ethyl-*p*-ethoxycinnamic acid
i) α,*m*-dimethylcinnamic acid
j) α,β-dibromo-β-*p*-fluorophenylpropionic acid
k) *o*-fluorophenylpropiolic acid
l) β-iodo-β-phenylpropionic acid

5. Outline a practical synthesis of the following from benzene, toluene, or benzaldehyde:

a) *o*-nitromandelic acid
b) *o*-chloromandelic acid
c) *o*-ethoxymandelic acid
d) ethyl *m*-methoxymandelate
e) *m*-aminomandelic acid
f) *m*-methylmandelamide
g) α-acetoxy-*m*-chlorophenylacetic acid
h) methyl *p*-chloromandelate
i) *m*-acetoxymandelic acid
j) α,*o*-dimethoxyphenylacetic acid

6. Describe a chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) benzylamine-*p*-carboxylic acid and N-methylbenzamide
b) *p*-N-methylaminobenzoic acid and N-methylbenzamide
c) phenylacetic acid and methyl benzoate
d) phthalic acid and terephthalic acid

e) cinnamic acid and phenylpropiolic acid
f) benzoic acid and *p*-ethoxybenzoic acid
g) benzoic acid and salicylic acid
h) ethyl benzoate and ethyl *n*-hexoate
i) benzamide and caproamide
j) benzoic acid and benzaldehyde
k)
l)
m)
n) mandelic acid and salicylic acid
o) mandelamide and salicylamide
p) salicylic acid and *p*-hydroxybenzoic acid

7. An aromatic hydrocarbon, *A*, $C_{10}H_{14}$, when heated under a reflux condenser with aqueous alkaline permanganate, slowly dissolves. When hydrochloric acid is added to the resulting liquid, cold, a solid, *B*, $C_8H_6O_4$, is precipitated. When *B* is heated, it is converted into *C*, $C_8H_4O_3$. There are four structurally isomeric monochloro derivatives of *A*. Write a possible structure for *A*. Are any other structures possible?

8. Compound *A*, C_7H_8O, is sparingly soluble in water, forming solution *B*. When aqueous bromine is added to *B*, the bromine color is discharged at once and a precipitate forms. When an excess of bromine is added, then sodium bisulfite in excess, compound *C*, $C_7H_5OBr_3$ is obtained. Compound *A* is readily soluble in aqueous sodium hydroxide, forming solution *D*. Ethyl iodide was added to *D* and enough ethyl alcohol to give a single phase. The mixture was heated for some time, and then most of the alcohol was removed by distillation. The organic phase, *E*, that separated was heated with an excess of alkaline permanganate. Addition of hydrochloric acid to a clear solution gave compound *F*, $C_9H_{10}O_3$. What deductions can be drawn from these statements? Show how they lead to a structure for *A*.

9. Compound *A*, $C_{10}H_{16}N_2$ is converted into *B*, $C_{12}H_{18}ON_2$, by acetic anhydride in excess. By the action of cold hydrochloric acid, sodium nitrite, and cuprous chloride, *A* is converted into *C*, $C_{10}H_{14}NCl$. Heating of *C* with aqueous alkaline permanganate in excess and then adding sulfuric acid in excess to the liquid after insoluble material has been removed by filtration causes a solid, *D*, to precipitate. This is *p*-chlorobenzoic acid. What deductions can be drawn from these statements? Show how they lead to a possible structure for *A*.

10. Compound *A*, $C_{11}H_{11}O_2Cl$, insoluble in water and in cold dilute aqueous acids and bases, dissolved slowly when heated under a reflux condenser with aqueous sodium hydroxide. Distillation through a fractionating column gave some liquid, *B*, distilling below 100°, and an aqueous solution, *C*, in the boiler. When a few drops of *B* was added to warm aqueous potassium triiodide and potassium carbonate, iodoform was precipitated.

Both *A* and *C* rapidly discharged the color of permanganate. Addition of hydrochloric acid to a part of *C* precipitated solid *D*, $C_9H_7O_2Cl$. Oxidation of another part of *C* with permanganate gave solid *E*, $C_7H_5O_2Cl$. There are two mononitro derivatives of *E* theoretically possible. What deductions can be drawn from these statements? Show how they lead to a formula for *A*.

CHAPTER 36

Quinones

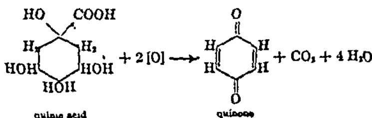
Quinones are oxidation products of dihydric or polyhydric phenols, according to the following general equation.



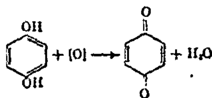
$$C_6H_4(OH)_2 + [O] \longrightarrow C_6H_4O_2 + H_2O$$

When there is only one benzene ring the hydroxyl groups must be in either the **ortho-** or **para-**positions. Although quinones are related chemically to phenols, structurally they are related to dihydrobenzene (cyclohexadiene, p. 95). Quinones are important because of the rapidity with which they react and because they are colored.

***p*-Benzoquinone, 1,4-O=C$_6$H$_4$=O.** This is commonly called **quinone.** It was first obtained (1838) from quinic acid (hence the name), the acid associated with the alkaloid, quinine, in the bark of the cinchona tree, by oxidation with manganese dioxide and dilute sulfuric acid.



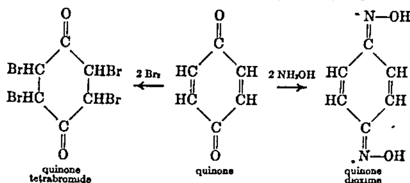
Quinone is conveniently prepared from hydroquinone by oxidation with ferric chloride or with dichromate and sulfuric acid. It is obtained quite pure by oxidation with bromate in dilute sulfuric acid, or by passing steam into a mixture of hydroquinone, manganese dioxide, and aqueous sulfuric acid. In this case the quinone steam distils. All these oxidations proceed rapidly.



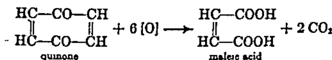
Quinone results also when a number of other *para*-substituted compounds are oxidized with dichromate and aqueous sulfuric acid, or manganese dioxide and aqueous sulfuric acid, for example, *p*-aminophenol, phenol-*p*-sulfonic acid, and sulfanilic acid. Phenol and aniline are oxidized by chromic acid, but somewhat more slowly, with quinone as one of the oxidation products. Quinone is produced technically by the electrolytic oxidation of benzene in the presence of sulfuric acid.

Quinone crystallizes in the form of golden yellow needles melting at 116°. It dissolves readily in alcohol, ether, or hot water, is volatile with steam, and has a pungent odor.

Structurally *p*-benzoquinone is 1,4-cyclohexadiene-3,6-dione. Two olefinic double bonds are indicated by the taking on of one mole and two moles of bromine (chlorine also) in chloroform solution to form quinone dibromide (dichloride) and quinone tetrabromide (tetrachloride), respectively. Two carbonyl groups are indicated by the formation of quinone monoxime and quinone dioxime with one and two moles of hydroxylamine, respectively.

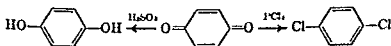


The formation of maleic acid by oxidation with potassium persulfate in the presence of silver sulfate and sulfuric acid is confirmation of this structure.



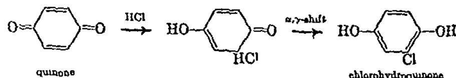
Quinone is thus an alicyclic rather than an aromatic compound, but because it is so readily obtained from hydroquinone, an aromatic compound, by oxidation; and is so readily converted into it and other aromatic compounds, the chemistry of quinones is profitably taken up in connection with aromatic compounds.

Quinone is not a true ketone. This is shown by numerous reactions, in particular those with reducing agents, phosphorus pentachloride, and hydrogen chloride. Reducing agents give hydroquinone (not 3,6-dihydroxy-1,4-cyclohexadiene), phosphorus pentachloride yields *p*-dichlorobenzene (not 3,3,6,6-tetrachloro-1,4-cyclohexadiene), and hydrogen chloride yields chlorohydroquinone.



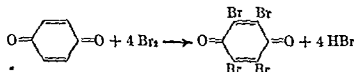
In addition to sulfurous acid, some of the reducing agents that rapidly reduce quinone to hydroquinone are: hydriodic acid, ferrous chloride, and sodium *hydrosulfite*. Quinone reduces ammoniacal silver ion to metallic silver.

The action of hydrogen chloride is explained as a 1,4-addition, hydrogen becoming attached to an oxygen atom, chlorine to a carbon atom. The resulting compound, by an α,γ-shift of a hydrogen atom, changes from a cyclohexadiene structure to a more stable benzene structure.



The reduction of quinone to hydroquinone may proceed also by a 1,4-addition.

Bromine in excess in acetic acid converts quinone to tetrabromoquinone. The reaction is complicated because hydrobromic acid produced by substitution adds to quinone, forming bromohydroquinone. However, intermediate products are converted finally to tetrabromoquinone (bromanil).

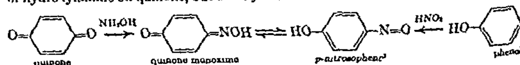


Tetrachloroquinone (chloranil) is formed similarly by the action of potassium chlorate and hydrochloric acid on quinone. This reagent converts many aromatic compounds to chloranil, for example, aniline, chloroanilins, phenols, chlorophenols, picric acid, and salicylic acid.

The Kekulé benzene structure is not present in the quinone molecule. The high reactivity of quinone and its lower stability, relative to most aromatic compounds, are indicative of a different structure. Although quinone can be steam distilled, it undergoes considerable decomposition when distilled at atmospheric pressure. The stabilization characteristic of the Kekulé benzene structure is lacking. The stabilization of quinone is that which characterizes conjugated systems in general. This is considerably less than that of benzene.

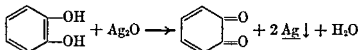
The bond arrangement in quinone is called **quinoid** or **quinonoid** to distinguish it from the **benzoid** or **benzenoid** arrangement characteristic of benzene. The quinonoid arrangement is found in a large number of dyes (Chap. 46), and thus is important in connection with color. The bond arrangement in *o*-benzoquinone produces a deeper color than that of *p*-benzoquinone, and is not as stable. These relationships hold in general.

Quinone Monoxime, $O{=}C_6H_4{=}NOH$. This is formed not only by the action of hydroxylamine on quinone, but also by the action of nitrous acid on phenol (p. 498).

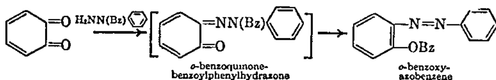


Although the product of each reaction is quinone monoxime, there appears to be some reversibility; in other words, quinone monoxime and *p*-nitrosophenol are tautomeric (p. 325). The formation of quinone dioxime by the action of a second mole of hydroxylamine points to the oxime structure, and the formation of *p*-nitrophenol by the oxidizing action of potassium ferricyanide points to the nitrosophenol structure.

***o*-Benzoquinone, 1,2-O=C_6H_4=O.** This can be obtained from pyrocatechol by careful oxidation in ether solution with silver oxide.



When freshly prepared at low temperature, *o*-quinone is colorless, but it soon changes into a red form which melts with decomposition at 60 to 70°. It is probable that the colorless form is a dimer or some other polymer. This quinone, like *p*-quinone, is easily reduced; for example, sulfurous acid or hydriodic acid reduces it to pyrocatechol. *o*-Benzoquinone reacts with benzoylphenylhydrazine, yielding a benzoylated hydroxyazo compound rather than a benzoylated hydrazone.

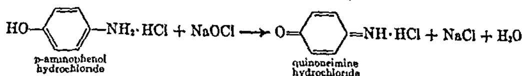


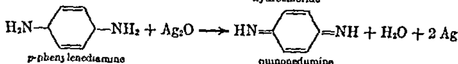
This shows that of the two isomeric forms, *o*-quinonephenylhydrazone and *o*-hydroxyazobenzene, the latter is the more stable. Its conjugated system is more stable than that of the hydrazone, owing no doubt to the presence of two benzenoid rings and the resulting greater stabilization through resonance.

Quinhydrone, $C_6H_4O_2 \cdot C_6H_4(OH)_2$. This is an addition compound of quinone and hydroquinone. It precipitates when aqueous solutions of the two compounds are mixed. It appears as an intermediate product in the reduction of quinone or in the oxidation of hydroquinone and is changed by continued reduction into hydroquinone and by continued oxidation into quinone. A convenient method of preparation is the oxidation of hydroquinone in aqueous solution with aqueous ferric chloride. Quinhydrone crystallizes as very dark green leaflets having a metallic luster and the odor of quinone. It appears to be formed when hydroquinone is used as a developer in photography.

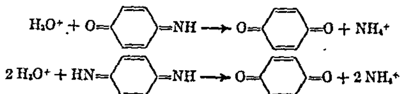
The quinone-hydroquinone system is rapidly reversible and is the best-known example of a considerable number of reversible oxidation-reduction systems of organic compounds. Since quinhydrone contains equal amounts of the oxidant and reductant, a suitable metallic electrode such as platinum dipping into an aqueous saturated solution of quinhydrone will acquire a potential which has a constant value at constant temperature and constant hydrogen-ion activity. This constitutes a quinhydrone half-cell. Since the electrode potential changes as the hydrogen-ion activity changes, quinhydrone is sometimes used as a means of determining the hydrogen-ion activity. It is superior in some respects to the hydrogen electrode because of the rapidity with which equilibrium is attained and because of the absence of appreciable salt effects. Substituted quinones form similar reversible systems.

Quinoneimines. Quinoneimine and quinonediimine are obtained from *p*-aminophenol and *p*-phenylenediamine, respectively, by carefully regulated oxidation with sodium hypochlorite, or with silver oxide.





These undergo rapid hydrolysis to *p*-benzoquinone in dilute aqueous acid, a reaction characteristic of imines (p. 393).



The oxidation of aniline and of *p*-phenylenediamine by chromic acid mixture to *p*-benzoquinone proceeds via the respective quinoneimine, which is readily hydrolyzed to the quinone in the acidic reaction mixture.

Quinoneimines, like the quinones, are unstable, and quite reactive. They are easily reduced, and suffer ring rupture on oxidation with permanganate. The respective reduction products are *p*-aminophenol and *p*-phenylenediamine. Imines probably are formed when these two compounds act as developers in photography. The monoimine is yellow, the diimine is colorless. They rapidly darken on exposure to air.

PROBLEMS

1. Describe a chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) quinone (*p*-benzoquinone) and hydroquinone
b) quinone and acetophenone
c) quinone and benzil
d) quinone and benzoin
e) quinone and benzophenone
f) quinone and biacetyl
g) quinone and chloranil
h) quinone and quinhydrone
i) hydroquinone and *p*-aminophenol
j) hydroquinone and benzoin
k) hydroquinone and dihydrobenzoin
l) hydroquinone and hydroquinone dimethyl ether
m) hydroquinone and quinhydrone
n) hydroquinone and resorcinol

2. Write the structural formulas of three different compounds that you predict can be oxidized to the following substance, and state the oxidizing agent that is preferred:

a) 2-methyl-1,4-benzoquinone
b) 2-chloro-1,4-benzoquinone
c) 2,5-dibromo-1,4-benzoquinone
d) 2,6-dimethyl-1,4-benzoquinone
e) 2-methyl-5-chloro-1,4-benzoquinone
f) 2-methoxy-1,4-benzoquinone
g) 1,4-benzoquinonecarboxylic acid
h) 2,6-dinitro-1,4-benzoquinone

CHAPTER 37

Biphenyl and Polyphenyl Compounds

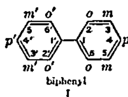
In this chapter are described a number of hydrocarbons having two o more complete rings; also, some of their derivatives. Some constants o

TABLE 94 **Physical Constants of Some Polyphenyl Compounds**

NAME	FORMULA	M.P. °C	B.P. °C	D_4^{20}
Biphenyl	$C_6H_5—C_6H_5$	70.0	254.9	1.155
1,4-Terphenyl	$C_6H_5—C_6H_4—C_6H_5$	210	383	
Diphenylmethane	$(C_6H_5)_2CH_2$	25.9	263.2	1.006
Triphenylmethane	$(C_6H_5)_3CH$	92.6	360	1.12
Tetraphenylmethane	$(C_6H_5)_4C$	282.5	429	
Hexaphenylethane	$(C_6H_5)_3C—C(C_6H_5)_3$	227		1.15 [a]
Triphenylchloromethane	$(C_6H_5)_3C—Cl$	112–113	230–235 [b]	
Triphenylcarbinol	$(C_6H_5)_3C—OH$	164.2	380	1.199 [a]

[a] At 0°. [b] At 20 mm.

these are listed in Table 94. The numbering of the different positions is shown for biphenyl by I.



biphenyl
I

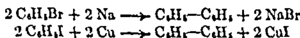
Similarly, whenever more than two benzene rings are attached to the same carbon atom, primed numbers and letters refer to the second benzene ring. Also, doubly primed numbers and letters are used for a third ring and triply primed for any fourth ring, as in triphenylmethane and tetraphenylmethane, respectively.

Biphenyl, Diphenyl, $C_6H_5—C_6H_5$. A convenient laboratory method of preparation consists in passing benzene slowly through an iron tube heated to redness. Benzene suffers dehydrogenation under these conditions.



$$2\,C_6H_6 \longrightarrow C_6H_5—C_6H_5 + H_2$$

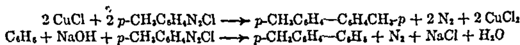
Although biphenyl can also be prepared by the action of metallic sodium on bromobenzene (Wurtz-Fittig synthesis, p. 428), a better method is that of Ullmann, *viz.*, the heating of iodobenzene with copper powder or copper bronze at 230°.



$$2\,C_6H_5Br + 2\,Na \longrightarrow C_6H_5—C_6H_5 + 2\,NaBr$$
$$2\,C_6H_5I + 2\,Cu \longrightarrow C_6H_5—C_6H_5 + 2\,CuI$$

The Ullmann reaction is very useful with substituted iodobenzenes — iodonitrobenzenes, in particular, because of the inertness of the nitro group towards metallic copper or copper bronze and of the activating effect of the nitro group on a halogen atom. Nitrobromo and even nitrochlorobenzenes react, especially when the nitro group is in the *ortho*-position. The carboxyl group also activates a halogen atom, for not only iodo- but also bromobenzoic acids undergo the Ullmann reaction and are an important source of symmetrical biphenyldicarboxylic acids.

Biphenyl and substituted biphenyls can be obtained through the *diazo reaction*. Decomposition of diazonium salts with cuprous chloride gives biphenyl compounds, as well as chloro compounds, in a Sandmeyer synthesis (p. 486) and with aqueous alkali and benzene gives biphenyl derivatives in the Gomberg reaction (p. 488).



$$2\,CuCl + 2\,p\text{-}CH_3C_6H_4N_2Cl \longrightarrow p\text{-}CH_3C_6H_4—C_6H_4CH_3\text{-}p + 2\,N_2 + 2\,CuCl_2$$
$$C_6H_6 + NaOH + p\text{-}CH_3C_6H_4N_2Cl \longrightarrow p\text{-}CH_3C_6H_4—C_6H_5 + N_2 + NaCl + H_2O$$

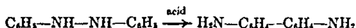
In the Gomberg reaction a large number of diazonium salts react with benzene, except those that readily undergo the azo coupling, for example, the one from *m*-phenylenediamine. The place of benzene can be taken by some other liquid compound, *viz.*, toluene, nitrobenzene, methyl benzoate, or phenol ethers. In these cases the Gomberg method usually gives a mixture of *ortho*- and *para*-isomers. The reaction takes place in the organic phase.

Biphenyl undergoes substitution readily, with formation of *para*-substituted products preferentially. Thus mononitration gives *o*-nitrobiphenyl and *p*-nitrobiphenyl, mainly the latter; nitration of *p*-nitrobiphenyl gives a mixture of *p,p'*-dinitrobiphenyl (63%) and *o,p'*-dinitrobiphenyl (37%). Biphenyl can also be chlorinated, brominated, or sulfonated. Oxidation of biphenyl with chromic anhydride in glacial acetic acid yields benzoic acid because one of the benzene rings undergoes destructive oxidation.

The spatial arrangement of the two benzene rings is established by the observation that both biphenyl and *p,p'*-dichlorobiphenyl have zero electric dipole moment. Thus in the molecule of each of these two compounds the two benzene rings lie on the same axis.

Preparation of Biphenyl Compounds. The main methods (already mentioned) are the Ullmann reaction (with copper powder), the reaction of diazonium salts with a cuprous compound (Sandmeyer reaction), and the reaction of diazonium salts with sodium hydroxide and an aromatic liquid (Gomberg reaction). Another synthetic method is the benzidine rearrangement of hydrazobenzenes.

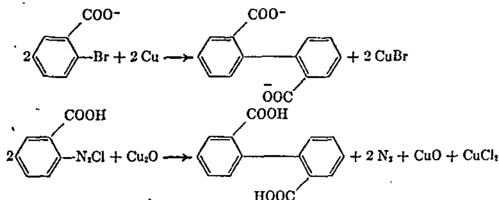
Benzidine, 4,4′-Diaminobiphenyl. This, one of the most important derivatives of biphenyl, is obtained by the rearrangement of hydrazobenzene (p. 466).



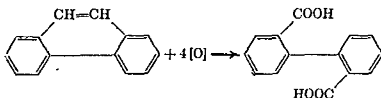
$$C_6H_5—NH—NH—C_6H_5 \xrightarrow{acid} H_2N—C_6H_4—C_6H_4—NH_2$$

Benzidine is important in connection with dye chemistry (Chap. 46). Either one or both of the amino groups may be diazotized and coupled with the same or different amine or phenol. Congo red is one of the best known dyes derived from benzidene. Benzidine forms a difficultly soluble sulfate and sometimes is used as a precipitant for sulfate ion, generally in alcoholic solution.

Diphenic Acid, 2,2′-Dicarboxybiphenyl. This may be synthesized by the standard methods, for example, from potassium *o*-bromobenzoate by heating with an excess of copper powder at 100° or from diazotized anthranilic acid by adding ammoniacal cuprous oxide.

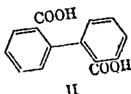


A usual method of preparation, however, is oxidation of phenanthrene or phenanthrenequinone (Chap. 39) with permanganate or chromic acid mixture.



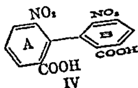
Diphenic acid is of interest because of the occurrence of an interesting type of stereoisomerism among certain of its derivatives.

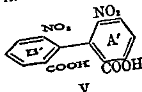
Stereoisomerism of Biphenyl Derivatives. Whereas diphenic acid, II, exists in only one form, a dinitro derivative, 6,6′-dinitro-2,2′-dicarboxybiphenyl, III, exists in two isomeric forms, which are optically active and therefore are mirror images of each other.



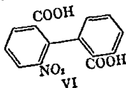


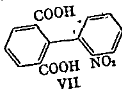
It is evident that the two benzene rings of III cannot lie in the same plane because if they did, it and its mirror image would be identical. Two possible space arrangements are shown by formulas IV and V, in which the rings *A* and *A′* are within the plane of the paper while *B* and *B′* are at right angles to it.





The existence of these two forms would not be predicted on the assumption that free rotation is possible about the single bond that joins the two rings. The existence of optical isomers shows that free rotation does not readily occur in this case. There is not enough space between the groups in the *ortho*-positions to permit the nitro group on ring *B* readily to slip past either the nitro or carboxyl group on ring *A*. When only one *ortho*-substituent is attached to each ring, free rotation is possible if the substituents are of average size, for example, Cl, CH_3, COOH, NH_2, and NO_2. In these cases the distance from the center of the *o*-carbon atom to the center of the substituent lies between 1.56 and 1.92 Å. But if the substituent is quite large, for example, iodine, or SO_3H, rotation apparently is restricted, for stereoisomeric forms are known. However, stereoisomerism is possible with two of the above five groups on one ring and only one on the other. This has been observed with 2,2′-dicarboxy-6-nitrobiphenyl (VI) and numerous other compounds, but not with 2,6-dicarboxy-2′-nitrobiphenyl (VII), because this is inactive on account of its symmetry.

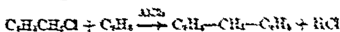




In stereoisomerism of this type the molecule does not possess an element of symmetry in spite of the fact that there is no asymmetric carbon atom. As a result, the compound and its mirror image are not identical. It is evident, therefore, that the condition necessary for optical isomerism is molecular asymmetry. It should be noted that for purposes of resolution the molecule should have an acidic or basic group.

It has been observed that the stability of an optically active form may vary from one that racemizes rapidly at room temperature to one that is quite stable. However, one of the latter type may racemize when heated. For example, VI racemizes slowly at 118°; the half-life period is 1.5 hours. Racemization of biphenyl compounds takes place when rotation about the C—C bond is possible. From data on half-life periods of a number of compounds, the relative effects of substituents in restricting rotation are: Br > CH_3 > Cl > NO_2 > COOH > OCH_3 > F.

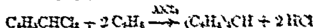
Diphenylmethane, $(C_6H_5)_2CH_2$, and Triphenylmethane, $(C_6H_5)_3CH$. These may be prepared by rather similar methods, for example, the Friedel-Crafts synthesis, the condensation of benzene with benzyl alcohol or benzaldehyde, respectively, and reduction of oxygen or halogen compounds.



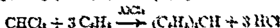
$$C_6H_5CH_2Cl + C_6H_6 \xrightarrow{AlCl_3} C_6H_5—CH_2—C_6H_5 + HCl$$



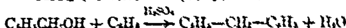
$$CH_2Cl_2 + 2\,C_6H_6 \xrightarrow{AlCl_3} C_6H_5—CH_2—C_6H_5 + 2\,HCl$$



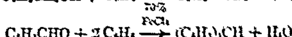
$$C_6H_5CHCl_2 + 2\,C_6H_6 \xrightarrow{AlCl_3} (C_6H_5)_3CH + 2\,HCl$$



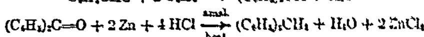
$$CHCl_3 + 3\,C_6H_6 \xrightarrow{AlCl_3} (C_6H_5)_3CH + 3\,HCl$$



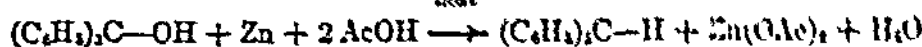
$$C_6H_5CH_2OH + C_6H_6 \xrightarrow[70\%]{H_2SO_4} C_6H_5—CH_2—C_6H_5 + H_2O$$



$$C_6H_5CHO + 2\,C_6H_6 \xrightarrow{FeCl_3} (C_6H_5)_3CH + H_2O$$



$$(C_6H_5)_2C{=}O + 2\,Zn + 4\,HCl \xrightarrow[heat]{amal.} (C_6H_5)_2CH_2 + H_2O + 2\,ZnCl_2$$



$$(C_6H_5)_3C—OH + Zn + 2\,AcOH \longrightarrow (C_6H_5)_3C—H + Zn(OAc)_2 + H_2O$$

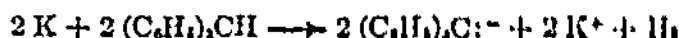


$$(C_6H_5)_3C—Cl + Zn + AcOH \longrightarrow (C_6H_5)_3C—H + ZnClOAc$$

Condensations proceed more readily when benzene is replaced by a compound having an *o,p*-orienting substituent, for example, methyl, methoxy, or dimethylamino. Reaction takes place mainly at the *para*-position.

Diphenylmethane is of minor importance, but triphenylmethane and its derivatives are important for a number of reasons, principally from the standpoint of free radical chemistry, chemistry of dyes, and theory of color. The two hydrocarbons undergo nitration, mainly to *para*-nitro derivatives. They undergo oxidation with chromic anhydride in glacial acetic acid, diphenylmethane to benzophenone, triphenylmethane to triphenylcarbinol. Vigorous oxidation yields benzoic acid with destruction of benzene rings.

Triphenylmethane has weakly acidic properties. When heated to 200° with metallic potassium in an inert atmosphere, it is converted into potassium triphenylmethyl.



$$2\,K + 2\,(C_6H_5)_3CH \longrightarrow 2\,(C_6H_5)_3C{:}^- + 2\,K^+ + H_2$$

This is an intensely red compound. A more convenient method is the reaction of triphenylmethyl with a solution of the metal in liquid ammonia (sodium reacts similarly). A deep red solution of sodium triphenylmethyl in ether is obtained from triphenylchloromethane and sodium amalgam. Potassium (or sodium) triphenylmethyl reacts rapidly and completely with moisture, forming colorless triphenylmethane.



$$H_2O + (C_6H_5)_3C{:}^- + K^+ \longrightarrow (C_6H_5)_3CH + K^+ + OH^-$$

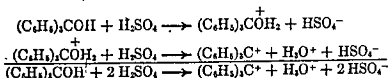
The most important derivatives of triphenylmethane are those having hydroxy, amino, or dimethylamino groups. They are important in dye chemistry; some members are described in Chapter 40.

Triphenylchloromethane, Triphenylmethyl Chloride, $(C_6H_5)_3CCl$. A convenient method of preparation of this colorless solid is a Friedel-Crafts synthesis from carbon tetrachloride and benzene. Only three of the four chlorine atoms are replaced by phenyl groups.



$$CCl_4 + 3\,C_6H_6 \longrightarrow (C_6H_5)_3CCl + 3\,HCl$$

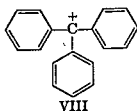
an intense yellow-colored solution. In 100 per cent sulfuric acid it has a van't Hoff i factor of 4, showing that a molecule of water is eliminated.



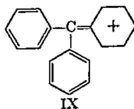
$$(C_6H_5)_3COH + H_2SO_4 \longrightarrow (C_6H_5)_3\overset{+}{C}OH_2 + HSO_4^-$$
$$(C_6H_5)_3\overset{+}{C}OH_2 + H_2SO_4 \longrightarrow (C_6H_5)_3C^+ + H_3O^+ + HSO_4^-$$
$$\overline{(C_6H_5)_3COH + 2\,H_2SO_4 \longrightarrow (C_6H_5)_3C^+ + H_3O^+ + 2\,HSO_4^-}$$

This indicates the formation of triphenylmethyl sulfate. With perchloric acid under anhydrous conditions a yellow solid, triphenylmethyl perchlorate, $(C_6H_5)_3C^+ + ClO_4^-$, can be obtained. When a base or even when enough water is added to these salts, colorless triphenylcarbinol is obtained. Triphenylcarbinol is called a **pseudo base** because, although not a base, it can form salts with acids. The positive ion in these salts is called a carbonium ion.

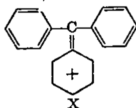
Positive and Negative Ions of Triphenylmethyl. The negative carbanion and positive carbonium ion of triphenylmethyl are quite stable, in contrast to aliphatic chemistry, where stable carbonium ions are not known, although they often are postulated as intermediates in reactions. Aliphatic carbanions are known (p. 85). The explanation of the stability of triphenylmethyl ions is made on the basis of resonance. The charge can resonate among the *ortho*- and *para*-positions of the three benzene rings, and the multiplicity of forms resulting from the resonance is largely responsible for the stability of the ion. The possibilities of resonance, in the case of the positive ion, are shown in VIII, IX, X, and XI.



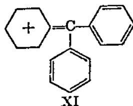
VIII



IX



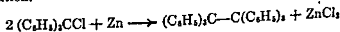
X



XI

There are eight resonance forms of VIII, arising from the Kekulé resonance of the three benzene rings. There are twelve resonance forms of each of IX, X, and XI, because the positively charged ring represents three resonance forms (p. 442), and these are multiplied twice by two, since each of the other two rings has two resonance forms. All told, there are forty-four resonance forms of either the positive or negative ion, but there are only eight resonance forms of triphenylmethane. The intensity of the color of the ion is ascribed to the distribution of the charge through resonance.

Hexaphenylethane, $(C_6H_5)_3C—C(C_6H_5)_3$, and Triphenylmethyl, $(C_6H_5)_3C$. Hexaphenylethane is formed by the action of zinc dust on triphenylmethyl chloride in benzene solution.



$$2\,(C_6H_5)_3CCl + Zn \longrightarrow (C_6H_5)_3C—C(C_6H_5)_3 + ZnCl_2$$

j) o,p′,p″-tribromotriphenylmethane
k) m,p′-dibromotriphenylmethane
l) p-chloro-p′-bromotriphenylmethane
m) m,p′-dimethyl-p″-bromotriphenylmethane
n) 1,2-diphenylethylene

4. Outline a practical laboratory preparation of the following, starting with benzene or toluene (assume that a *para*-acid can be obtained pure from an *ortho,para*-mixture):

a) o-methylbiphenyl
b) m-nitrobiphenyl
c) m-iodobiphenyl
d) o-nitrobiphenyl
e) 2,4-dichlorobiphenyl
f) 2,4-dibromobiphenyl
g) 2-bromo-4-methylbiphenyl
h) 3-bromo-4-methylbiphenyl
i) 2,4′-dibromobiphenyl
j) 3,4′-dibromobiphenyl
k) 4-bromo-4′-carboxybiphenyl
l) 4-carboxy-4′-methylbiphenyl

5. Outline a practical laboratory preparation, from compounds of fewer carbon atoms, of:

a) 4,4′-dimethyltriphenylmethane
b) 4-methyl-4′,4″-dichlorotriphenylmethane
c) 4-chloro-4′,4″-dimethyltriphenylmethane
d) 4,4′-bisdimethylaminotriphenylmethane
e) 4-methoxy-4′,4″-bisdimethylaminotriphenylmethane
f) 3-nitro-4′,4″-dibromotriphenylmethane
g) 4,4′,4″-trimethyltriphenylmethane
h) 4,4′-dimethoxytriphenylmethane
i) 3-chloro-4′,4″-diethoxytriphenylmethane
j) 2,2′,4,4′,4″-pentamethyltriphenylmethane
k) 1,1,1,p,p′-pentachloro-2,2-diphenylethane
l) 1,1,1-trichloro-2,2-di-p-tolylethane

6. Compound *A*, $C_{14}H_{10}O_4NCl$, is insoluble in water or in dilute aqueous acid or base. With 2,4-dinitrophenylhydrazine in hot acetic acid *A* gives compound *B*. When *A* is oxidized with dilute nitric acid, compound *C*, $C_{14}H_8O_4NCl$, is formed. When heated with alkaline permanganate, *C* slowly dissolves. From the reaction mixture *m*-nitrobenzoic acid and *p*-chlorobenzoic acid can be isolated. What deductions can be drawn from these statements? Show how they lead to a structure for *A*.

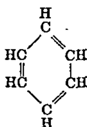
CHAPTER 38

Naphthalene

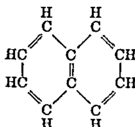
Two benzene rings are said to be fused when they have two carbon atoms in common. A number of hydrocarbons having fused rings are found in coal tar, the simplest being naphthalene.

Naphthalene, $C_{10}H_8$. This is a constituent of coal tar, from which it is obtained by fractional distillation. The amount varies from 5 to 10 per cent. It is formed by the action of intense heat upon various carbon compounds, hence its occurrence in coal tar. It crystallizes well from alcohol in the form of shining, colorless plates. It has an appreciable vapor pressure and sublimes slowly at room temperature, more rapidly when heated, and distils with steam. Its odor is characteristic.

In 1866, one year after Kekulé proposed his cyclic structure of benzene, I, Erlenmeyer proposed II as the structure of naphthalene.



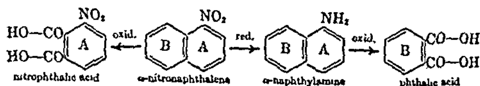
Kekulé's benzene formula
I



Erlenmeyer's naphthalene formula
II

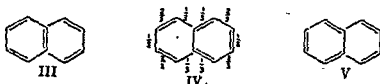
The correctness of the fused-ring structure of naphthalene was subsequently established by different investigations. Oxidation methods are especially valuable. Naphthalene is converted into 1,4-naphthoquinone and phthalic acid when oxidized with chromic anhydride in acetic acid. α-Nitronaphthalene, formed from naphthalene by nitration, is converted into 3-nitrophthalic acid on oxidation. These results point to the presence in naphthalene of a benzene ring, to which are attached a nitrogen atom (in the form of the nitro group) and two side chains *ortho* to each other. This nitronaphthalene is converted into α-aminonaphthalene on reduction, and the latter when oxidized yields phthalic acid, not aminophthalic acid. This indicates that in the mole-

cule of naphthalene there is a second benzene ring, and to this are attached two side chains *ortho* to each other, but no nitrogen atom. Thus the benzene ring holding the nitrogen atom has been lost during the second oxidation. The changes shown below account satisfactorily for these observations. In



the oxidation of nitronaphthalene, ring *A* carrying the nitro group remains intact, and ring *B* is destroyed, while in the oxidation of aminonaphthalene, ring *A* carrying the amino group is destroyed, and ring *B* remains intact. It is concluded from this that a nitro group makes the benzene ring more resistant to oxidation. It is known that an amino (or hydroxyl) group makes it more susceptible to oxidation (pp. 477, 498).

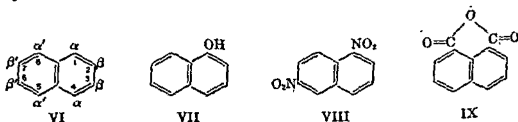
There are three resonance forms of naphthalene, III, IV, and V.



These are believed to contribute approximately equally to the structure of the molecule. On this account, of the eleven C—C bonds in the naphthalene nucleus, seven have approximately $\frac{1}{3}$ double bond character and four have approximately $\frac{2}{3}$ double bond character, as shown by IV. Some of the reactions of naphthalene derivatives have been accounted for on this basis.

Naphthalene is an important industrial chemical. It has been used for decades as a repellent for moths in the form of moth balls. Its main uses chemically are for the production of phthalic anhydride (p. 530), the naphthols, and the naphthylamines. The last two find extensive application in the dye industry. The K vitamins are derivatives of naphthaquinone.

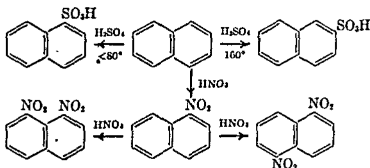
Nomenclature and Isomerism. The positions in naphthalene are shown by VI.



There are only two monosubstitution products, the α and β, because the α- and α'-positions are equivalent, and so are the β and β'. There are ten di-

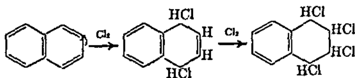
substitution products predicted by the structure when the two substituents are alike. Just ten dichloronaphthalenes are known. Monosubstitution products usually are indicated as α or β, others by numerals. For example, VII is α-naphthol and VIII is 1,6-dinitronaphthalene. Positions 1 and 8 are related to each other much like *ortho;* they are called *peri.* Other rings may originate here; for example, IX is naphthalic anhydride

Reactions. Naphthalene, like benzene, undergoes substitution and oxidation. The reactions proceed more readily with naphthalene. Condensation reactions also take place. Substitution proceeds more readily at the α-position. For example, nitration with dilute nitric acid or with fuming nitric acid in glacial acetic acid yields α-nitronaphthalene. Sulfonation at temperatures up to 80° yields chiefly naphthalene-α-sulfonic acid, and at 150 to 160° chiefly naphthalene-β-sulfonic acid. At higher temperatures disulfonic acids are obtained.



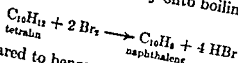
Nitration of α-nitronaphthalene takes place on the second benzene ring, with formation of 1,5- and 1,8-dinitronaphthalenes, and from the reaction mixture obtained by the action of chlorine, 5-chloro-1-nitro- and 8-chloro-1-nitronaphthalene can be obtained. In addition to the fact that an α-position is more reactive than a β-position, it is evident that a second substitution takes place in the second ring when a deactivating *meta*-orienting group is already present.

Chlorination is more complicated, and is known to proceed in steps. Chlorine gas at room temperature first adds to naphthalene, forming a mixture of naphthalene dichloride and naphthalene tetrachloride, the addition taking place entirely on one benzene ring.



These two compounds lose hydrogen chloride when heated, or better, when boiled with alcoholic potash, and are converted into monochloro- and dichloronaphthalene, respectively. The first gives α-chloronaphthalene, the second a mixture of three different isomers, 1,3-, 1,4-, and 2,3-dichloronaphthalenes. The corresponding bromine addition compounds are less stable, and of these

utilized. Bromine is allowed to fall slowly onto boiling tetralin; the reaction takes place in the vapor.



$$\underset{\text{tetralin}}{C_{10}H_{12}} + 2\,Br_2 \longrightarrow \underset{\text{naphthalene}}{C_{10}H_8} + 4\,HBr$$

Naphthalene, compared to benzene, undergoes substitution, oxidation, and reduction more readily. Thus it acts as if it were less saturated than benzene.

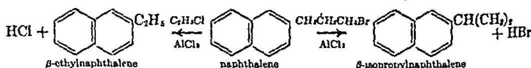
Chloronaphthalenes, $C_{10}H_7Cl$. The α-isomer is obtained from naphthalene by direct chlorination, as described above, the β-isomer from β-naphthylamine through the diazo reaction (p. 486). Bromonaphthalenes are obtained similarly.

TABLE 95 | Some Naphthalene Compounds

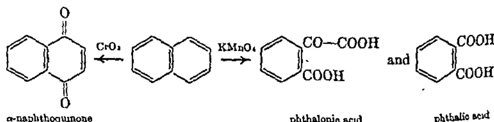
NAME	M.P. °C	B.P. °C
Naphthalene	80.3	218
α-Methylnaphthalene	−22	241
β-Methylnaphthalene	37–38	240–242
α-Bromonaphthalene	6.2	281
β-Bromonaphthalene	59	281–282
α-Chloronaphthalene		263
β-Chloronaphthalene	46	
α-Naphthalenesulfonic acid	90	$K_a = 1.8 \times 10^{-4}$
[illegible]aphthalenesulfonic acid	91	$K_a = 2.5 \times 10^{-4}$
[illegible]phthol	96	280
[illegible]ol	122	286
[illegible]thoquinone	115–120 dec.	
[illegible]hoquinone	125	
[illegible]ine	50	300.8
[illegible]	113	294
[illegible]	61.5	304
[illegible]	79	

only the tetrabromide can be isolated under regulated conditions. The products of the action of bromine are first α-monobromonaphthalene and later a variety of disubstitution products. The bromination reaction proceeds so readily that hydrogen bromide may be conveniently prepared by dropping bromine upon naphthalene.

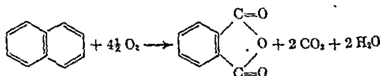
Naphthalene undergoes alkylation but not with methyl halides. Ethyl chloride yields β-ethylnaphthalene in the Friedel-Crafts reaction, and higher alkyl halides also yield mainly the β-isomer.



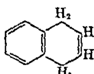
Naphthalene undergoes oxidation more readily than benzene. With chromic anhydride in glacial acetic acid it yields α-naphthoquinone, and with potassium permanganate under alkaline conditions it yields phthalonic and phthalic acids.



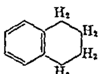
Air oxidation over vanadium pentoxide converts naphthalene to phthalic anhydride. An important industrial process is based on this reaction.



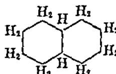
Naphthalene is more easily reduced than is benzene. With metallic sodium and boiling ethanol, one molecule of hydrogen is added by 1,4-addition; with boiling amyl alcohol and sodium, or with hydrogen and a nickel catalyst, tetralin is formed by the addition of two molecules of hydrogen to one ring. With a more active catalyst naphthalene is completely hydrogenated by the addition of five molecules.



1,4-dihydronaphthalene



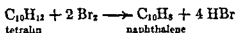
tetralin
1,2,3,4-tetrahydronaphthalene



decalin
decahydronaphthalene

Tetralin is useful in the preparation of hydrogen bromide, because the hydrocarbon is converted to naphthalene, thus allowing all of the bromine to be

utilized. Bromine is allowed to fall slowly onto boiling tetralin; the reaction takes place in the vapor.



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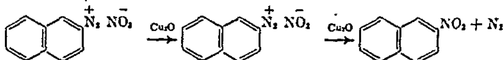
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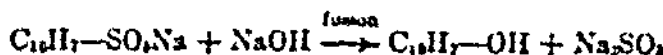
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[a] Dihydrate.

Nitronaphthalenes, $C_{10}H_7NO_2$. Since the usual methods of nitrating naphthalene give only the α-isomer, the β-isomer can be obtained only indirectly. It is prepared from β-naphthylamine by diazoting in nitric acid solution and adding cuprous oxide.



Naphthalenesulfonic Acids, $C_{10}H_7SO_3H$. α-Naphthalenesulfonic acid is the main product when naphthalene is sulfonated at temperatures of 80° or lower, β-naphthalene sulfonic acid at 160° or higher (p. 559). The α-isomer, when heated at 160° with sulfuric acid, is converted into the β-isomer. The main use of these products is in the production of the corresponding naphthols (hydroxynaphthalene) by fusion with a base.



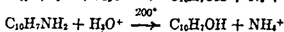
$$C_{10}H_7{-}SO_3Na + NaOH \xrightarrow{\text{fusion}} C_{10}H_7{-}OH + Na_2SO_3$$

Sulfonation of a naphthalenesulfonic acid takes place in the other benzene ring; from the β-acid, by heating on a water bath with fuming sulfuric acid, naphthalene-1,6-disulfonic acid is formed. With concentrated sulfuric acid at 160 to 180° are obtained the 2,6-, the 2,7-, and some of the 1,6-disulfonic acids.

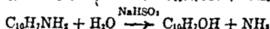
Naphthols, $C_{10}H_7OH$; α-Naphthol (1-Naphthol) and β-Naphthol (2-Naphthol). These are minor constituents of coal tar. In addition to the alkali fusion of a naphthalenesulfonate, a naphthol may be obtained from the corresponding naphthylamine through the diazo reaction, or by heating it at 200° under pressure for many hours with dilute aqueous sulfuric acid having an equimolar amount of the acid (an industrial method) or, more conveniently for laboratory work, by heating it with aqueous sodium bisulfite (Bucherer reaction).



$$C_{10}H_7N_2Cl + H_2O \longrightarrow C_{10}H_7OH + N_2 + HCl$$



$$C_{10}H_7NH_2 + H_3O^+ \xrightarrow{200^\circ} C_{10}H_7OH + NH_4^+$$

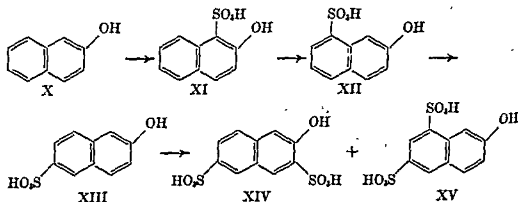


$$C_{10}H_7NH_2 + H_2O \xrightarrow{NaHSO_3} C_{10}H_7OH + NH_3$$

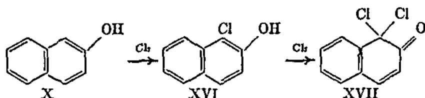
The Bucherer reaction proceeds more readily when a sulfonic acid group is *para* to the amino group. The reaction is useful in the conversion of naphthionic acid (p. 564) to α-naphthol-4-sulfonic acid (Neville-Winther acid).

The naphthols are less soluble in water than is phenol and are readily soluble in alcohol or ether. As acids they are similar to phenol, and dissolve readily in aqueous sodium hydroxide (K_a, 1.1×10^{-10}, 2.1×10^{-10}, and 1.2×10^{-10}, respectively, for phenol, α-naphthol, and β-naphthol).

The main nonionic reactions of naphthols are substitution (including azo coupling), oxidation, and replacement of the hydroxyl group. α-Naphthol substitutes easily in the 2- and 4-positions; β-naphthol first in the 1-position. Chlorination, bromination, or nitration of β-naphthol under the proper conditions gives first the 1-substituted-2-naphthol; the position taken on second bromination or nitration is the 6-position, and this is true also of chlorination, when done in sunlight. Sulfonation of β-naphthol, X, is interesting. The first product, 2-naphthol-1-sulfonic acid, XI, is unstable in contact with sulfuric acid and changes to 2-naphthol-8-sulfonic acid, crocein (Baeyer) acid, XII. This in turn, in contact with sulfuric acid, changes partly to 2-naphthol-6-sulfonic acid (Schaeffer acid), XIII, in the cold, and completely when warmed to 60°. Schaeffer acid on further sulfonation yields 2-naphthol-3,6- and 2-naphthol-6,8-disulfonic acids (G-acid, XIV, and R-acid, XV, respectively).



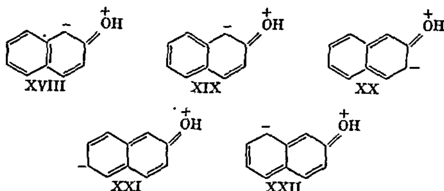
Chlorination of β-naphthol, X, gives first 1-chloro-2-naphthol, XVI, and then 1,1-dichloro-2-keto-1,2-dihydronaphthalene, XVII, especially if sodium acetate is present.



This result can be explained as addition of chlorine to the 1,2-double bond of β-naphthol, followed by loss of hydrogen chloride from the addendum. It is shown on page 558 that the 1,2-C—C bond of naphthalene has $\frac{2}{3}$ double-bond character, while the 2,3-C—C bond has $\frac{1}{3}$ double-bond character. Another explanation is given later.

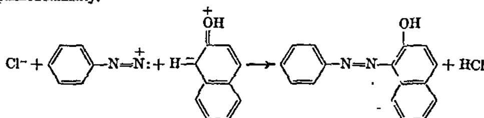
Coupling with diazonium salts takes place readily with formation of intensely colored azo compounds. Coupling with α-naphthol takes place mainly in the 4-position, if it is free, otherwise in the 2-position; with β-naphthol only in the 1-position. Some sulfonated α-naphthols react in the 2-position. The reactions are often used for the detection of small amounts of primary aromatic amines. They are important in dye chemistry, for many of the azo dyes so formed find application in the dye industry. *Naphtholsulfonic acids are important intermediates for many of these.*

The fact that β-naphthol usually substitutes first in the 1-position and couples only in the 1-position can be explained in the same terms as the *ortho,para*-orientation of phenol. In addition to the three Kekulé structures corresponding to X, the activated resonance forms of β-naphthol are XVIII, XIX, XX, XXI, and XXII.



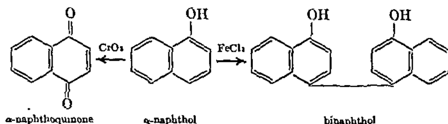
It is seen that the distribution of negative charge favors the 1-position over the 3-, 6-, and 8-positions. Therefore, the activation energy needed for reaction in the 1-position is the lowest. It was noted that 2-naphthol-1-sulfonic acid rearranges to 2-naphthol-8-sulfonic and this to 2-naphthol-6-sulfonic acid, but not to 2-naphthol-3-sulfonic acid. It is noted later that 1,2-naphthoquinone is more stable than 2,6-naphthoquinone and that 1,7- and 2,3-naphthoquinones do not exist. Therefore, the contribution of XX to the overall structure of β-naphthol must be quite small indeed since it represents a system of higher energy than the others.

The coupling of β-naphthol with diazonium salts exclusively in the 1-position explained similarly.



Here the positive benzene diazonium ion, reacting as one of the resonance forms (p. 485), forms a bond at the position of maximum negative charge.

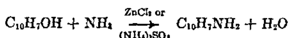
Oxidation of α-naphthol with chromic anhydride in glacial acetic acid gives a little α-naphthoquinone, along with other products. Both α- and β-naphthols reduce ammoniacal silver solution, and both in aqueous solution are converted to binaphthols by ferric chloride.



α-naphthoquinone α-naphthol binaphthol

Each yields phthalonic acid with permanganate, and finally phthalic acid.

The hydroxyl group is replaced by the amino group when the naphthol is heated under pressure with ammonia in the presence of zinc chloride or, more easily, when heated at temperatures of 100 to 150° with ammonia in the presence of ammonium sulfite (Bucherer reaction).



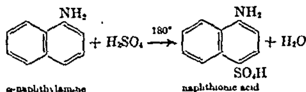
$$C_{10}H_7OH + NH_3 \xrightarrow[(NH_4)_2SO_3]{ZnCl_2 \text{ or}} C_{10}H_7NH_2 + H_2O$$

The latter (Bucherer) reaction is thus seen to be reversible.

Naphthylamines, $C_{10}H_7NH_2$. The α-isomer is obtained by reduction of α-nitronaphthalene or ammonolysis of α-naphthol, the β-isomer by ammonolysis of β-naphthol. The ammonolysis may be effected by heating with ammonia in the presence of zinc chloride, but preferably by the Bucherer reaction.

Naphthylamines are weaker bases than aniline ($K_b = 1 \times 10^{-10}$ and 2×10^{-10}, respectively, for α- and β-naphthol) and dissolve in dilute aqueous hydrohalic acids. They can be diazotized, and the diazonium salts couple readily with phenols and aromatic amines. Diazonium salts are relatively stable, especially the sparingly soluble ones, such as those prepared with sulfuric or naphthalene sulfonic acids. Some can be boiled with water without decomposition.

Naphthylamines undergo coupling in a manner similar to that of the naphthols. When coupled with a diazonium salt, α-naphthylamine reacts at the 4-position if it is free, otherwise at the 2-position; β-naphthylamine reacts only at the 1-position. Naphthylamine sulfonic acids are more valuable than the unsubstituted amines in the dye industry. One of the most important ones is naphthionic acid, 1-amino-4-sulfonaphthalene. It is prepared like sulfanilic acid (p. 479), by heating equimolar amounts of α-naphthylamine and sulfuric acid at 180 to 200

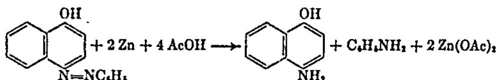


α-naphthylamine naphthionic acid

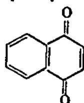
A number of sulfonated naphthols and naphthylamines are listed in Table 95.

Aminonaphthols and diaminonaphthalenes are often obtained by reduction of a

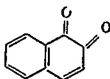
suitable hydroxyazo or aminoazo compound. As an example, 1-hydroxy-4-aminonaphthalene is obtained by reduction of benzene-azo-α-naphthol.



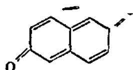
Naphthoquinones, $C_{10}H_6O_2$. Of the six structurally possible naphthoquinones only three are known, *viz.*, α-naphthoquinone (1,4-), β-naphthoquinone (1,2-), and *amphi*-naphthoquinone (2,6-).



alpha-



beta-



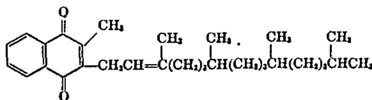
amphi-

The *alpha*-isomer results from oxidation of naphthalene, α-naphthol or 1,4-dihydroxynaphthalene (p. 542); the *beta*-isomer can be obtained by the oxidation of 1-amino-2-naphthol or 1,2-dihydroxynaphthalene with aqueous dichromate under acid conditions; the *amphi*-isomer from 2,6-dihydroxynaphthalene with lead dioxide. The *alpha*- and *beta*-isomers are analogous to *para*- and *ortho*-benzoquinone, respectively. The *alpha* is yellow, the *beta* crystallizes as red needles from ether, and the *amphi* is yellowish red. The *alpha*-isomer is volatile with steam, the other two are nonvolatile with steam. Oxidation of α-naphthoquinone with permanganate under acidic conditions at 40° gives an almost quantitative conversion to phthalic acid; oxidation of β-naphthoquinone in sodium bicarbonate solution gives phthalonic acid.

The ease of reduction of the three quinones is in the order: *amphi* and $\beta > \alpha$. This is shown by their action towards reducing agents: hydriodic acid alone reduces the 1,2- and 2,6-isomers, but hydriodic acid and red phosphorus are needed to reduce the 1,4-isomer; sulfurous acid readily reduces the 1,2-quinone smoothly to 1,2-dihydroxynaphthalene and the 2,6-quinone to a green, insoluble product, but the 1,4-isomer only at high temperature.

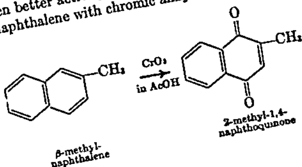
The relative stabilities of the naphthoquinones can be accounted for on the basis of resonance structures and of relative stabilities of *o*- and *p*-quinone rings (p. 544). Thus for 1,4-naphthoquinone there are two Kekulé forms and a *p*-quinone ring; for 1,2-naphthoquinone there are two Kekulé forms and an *o*-quinone ring; and for 2,5-naphthoquinone, only one resonance form and two *p*-quinone rings. Other possible quinone structures (nonexistent) have only one resonance form and either one *o*-quinone ring (1,7-) or two *o*-quinone rings (1,5- and 2,3-naphthoquinone).

An interesting derivative is **vitamin K_1**, 2-methyl-3-phytyl-1,4-naphthoquinone.



vitamin K_1

The phytyl radical is the radical of phytyl alcohol (p. 649) and is found in chlorophyll (p. 669). A deficiency of vitamin K causes hemorrhages of the skin and other tissues, owing to a lowered tendency of the blood to coagulate. It has been designated as the "koagulations vitamin." Some other derivatives of naphthoquinone have vitamin K activity, among them 2-methyl-1,4-naphthoquinone, sometimes called menadione, with even better activity than vitamin K_1. It is prepared easily by oxidation of β-methylnaphthalene with chromic anhydride in glacial acetic acid.



PROBLEMS

1. Predict the theoretically possible isomeric (including any stereoisomeric):
   a) dibromonaphthalenes
   b) trichloronaphthalenes
   c) chloro-α-methylnaphthalenes
   d) chloronitronaphthalenes
   e) dinaphthylethanes
   f) dinaphthylethylenes
   g) *sec*-butylnaphthalenes
   h) di-*sec*-butylnaphthalenes
   i) chlorodinitronaphthalenes
   j) chlorobromonitronaphthalenes
   k) chloro-α-ethylnaphthalenes
   l) dichloro-α-ethylnaphthalenes

2. Starting with naphthalene, show the steps involved in the preparation of:
   a) naphthionic acid
   b) 1-naphthol-4-sulfonic acid
   c) 2,4-dibromo-1-naphthol
   d) 2,4-dinitro-1-naphthol
   e) 1,4-dihydroxynaphthalene
   f) 1-amino-2-hydroxynaphthalene
   g) 1,5-dinitronaphthalene
   h) 1,5-diaminonaphthalene
   i) 5-bromo-α-naphthylamine
   j) 2,6-dihydroxynaphthalene
   k) 1,2-diaminonaphthalene
   l) 1,7-dihydroxynaphthalene

3. Describe a convenient chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:
   a) naphthalene and diphenylmethane
   b) naphthalene and durene
   c) naphthalene and α-nitronaphthalene
   d) α-nitronaphthalene and α-naphthylamine
   e) α-nitronaphthalene and β-naphthylamine
   f) naphthalene and α-naphthol
   g) naphthalene and β-naphthol
   h) naphthalene and 1,4-naphthoquinone
   i) naphthalene and α-naphthylamine
   j) 1,4-naphthoquinone and hydroquinone
   k) naphthionic acid and sulfanilic acid
   l) naphthionic acid and α-benzenesulfonamidonaphthalene
   m) α-acetamidonaphthalene and 5-amino-1-acetylnaphthalene
   n) β-naphthol and β-acetoxynaphthalene

4. State the aromatic acid or acids you predict to be the result of oxidation of the following with permanganate:

a) α-cyanonaphthalene
b) β-cyanonaphthalene
c) 1-amino-5-nitronaphthalene
d) 1-amino-8-nitronaphthalene
e) naphthalene-1-N,N-dimethylsulfonamide
f) naphthalene-2-N,N-diethylsulfonamide
g) 4-nitro-α-naphthol
h) α-naphthol-4-sulfonic acid
i) 5-nitro-α-naphthol
j) 8-nitro-α-naphthol

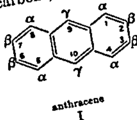
5. Compound *A*, $C_{12}H_{11}O_2N$, is insoluble in water or in aqueous acids or bases. It slowly dissolves when heated with tin and hydrochloric acid. After the soluble tin has been precipitated by hydrogen sulfide, addition of excess base to the solution causes compound *B*, $C_{12}H_{13}N$, to separate. When *A* and *B* are separately oxidized with permanganate, *A* yields 3-nitrophthalic acid and *B*, benzene-1,2,4-tricarboxylic acid. Show how a structure for *A* can be deduced from these statements.

6. Compound *A*, $C_{11}H_7O_4N$, insoluble in water and in dilute hydrochloric acid, dissolves in aqueous sodium carbonate; it also reacts readily with ammonium sulfide, yielding *B*, $C_{11}H_9O_2N$. When *A* and *B* are heated separately with an excess of aqueous alkaline permanganate, a dark precipitate forms. From the respective solutions, after filtration, excess of hydrochloric acid causes the separation of 4-nitro-1,2,3-tricarboxybenzene from *A* and phthalic acid from *B*. Show how these facts lead to a structure for *A*.

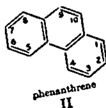
CHAPTER 39

Anthracene and Phenanthrene

Anthracene and phenanthrene are constituents of coal tar (about 0.5 and 1–2%, respectively). One of the most important naturally occurring derivatives of anthracene is the dye alizarin (p. 574). A large number of important synthetic dyes are related to anthracene. The phenanthrene structure is important in connection with carcinogenic hydrocarbons and also because the carbon skeleton of a large number of important natural products is related to the phenanthrene ring system (p. 575). Anthracene and phenanthrene are isomeric hydrocarbons, I and II.

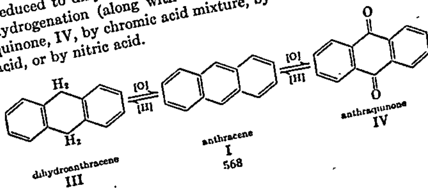


anthracene
I



phenanthrene
II

Anthracene and Phenanthrene, $C_{14}H_{10}$ (Gr. *anthra*, carbon). Both these crystallize in plates. Anthracene shows a bluish violet fluorescence in the solid and a violet one in solution; phenanthrene, bluish in solution. Each forms a solid addition compound with picric acid; anthracene, ruby red needles, m.p. 152°; phenanthrene, golden yellow needles, m.p. 144°. Anthracene when exposed to light in solution dimerizes to dianthracene. Anthracene can be reduced to dihydroanthracene, III, by sodium amalgam and alcohol or by hydrogenation (along with other products). It can be oxidized to anthraquinone, IV, by chromic acid mixture, by chromic anhydride in glacial acetic acid, or by nitric acid.

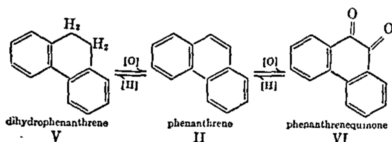


dihydroanthracene
III

anthracene
I

anthraquinone
IV

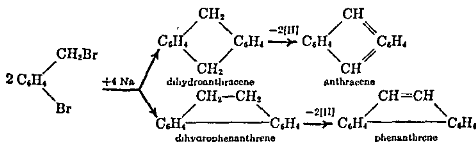
The reverse changes are possible: III is oxidized to IV with chromic acid, and IV, when heated with zinc dust or when heated with hydriodic acid and red phosphorus in a sealed tube, is reduced to I. Phenanthrene, II, is reduced to dihydrophenanthrene, V, by metallic sodium in boiling amyl alcohol (but not by sodium amalgam in boiling ethyl alcohol) or by hydrogenation (along with other products). It can be oxidized to phenanthrenequinone, VI, by chromic acid mixture, by chromic anhydride in glacial acetic acid, or by hydrogen peroxide in acetic acid.



Oxidizing agents convert V to VI; the latter yields II when it is heated with zinc dust.

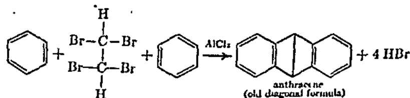
Structures of Anthracene and Phenanthrene. A structure established for the dihydrohydrocarbon or the quinone can be extended to the hydrocarbon itself, in view of the relationships just mentioned.

1. In a Wurtz-Fittig synthesis, *o*-bromobenzyl bromide is converted, by the action of metallic sodium, into a complex mixture containing anthracene (*ca.* 20% conversion) and some phenanthrene (*ca.* 3%), or the 9,10-dihydro derivatives of these. The products actually identified were the quinones, obtained by oxidation.



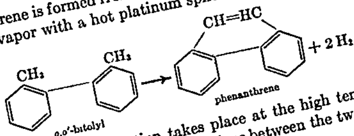
These results show that in the molecules of anthracene and phenanthrene there are two benzene rings with two connections between them at the *ortho*-positions. No decision can be made in regard to which structure applies to either one.

2. Anthracene, along with other products, is formed from benzene and acetylene tetrabromide, in a Friedel-Crafts synthesis.



This shows that there are two benzene rings attached to each other through two methine groups, but gives no information as to the actual points of union. They are assumed to be *ortho*. The diagonal formula at one time was considered established by this synthesis but at the present time is given little weight.

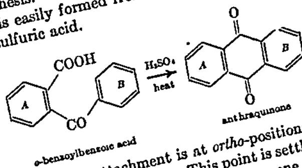
3. Phenanthrene is formed from *o,o'*-bitolyl (*o,o'*-dimethylbiphenyl) by long contact of its vapor with a hot platinum spiral.



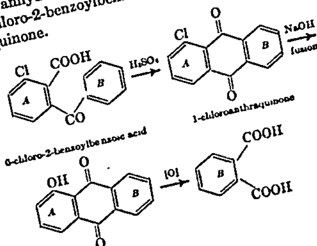
Unless some sort of isomerization takes place at the high temperature, this reaction shows that one of the two connections between the two benzene rings in the phenanthrene molecule is a direct bond.

4. Structures of anthraquinone and phenanthrenequinone have been established unequivocably, anthraquinone by synthesis, phenanthraquinone by oxidation and synthesis.

Anthraquinone is easily formed from *o*-benzoylbenzoic acid (p. 531) when it is heated with sulfuric acid.

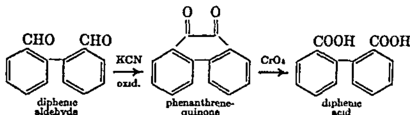


This shows that in ring *A* attachment is at *ortho*-positions, but does not establish the relative positions on ring *B*. This point is settled by starting with 3-chlorophthalic anhydride, condensing it with benzene in a Friedel-Crafts reaction to 6-chloro-2-benzoylbenzoic acid, then closing the ring to form 1-chloroanthraquinone.



When this is fused with alkali, the chloro group is replaced by the hydroxyl group, yielding 1-hydroxyanthraquinone, and when this is oxidized, phthalic acid is obtained. Ring *A* holding the hydroxyl group is oxidized away. Thus the attachments to ring *B* also are *ortho* to each other.

One of the simpler syntheses of phenanthrenequinone is from biphenyl-*o,o'*-dialdehyde (diphenic aldehyde) by an intramolecular benzoin condensation (p. 518) in an alcoholic solution of potassium cyanide. The benzoin first formed undergoes oxidation to the quinone during crystallization.

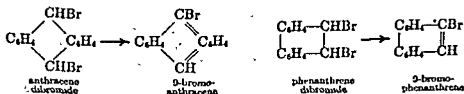


This synthesis shows that one of the connections between the two benzene rings in phenanthrenequinone is a direct one. This is substantiated by oxidation of the quinone to diphenic acid (p. 549), a reaction known long before the synthesis. Thus the various degradative and synthetic methods described are in agreement regarding the structures of anthracene and phenanthrene.

Consideration of the structures of anthracene and phenanthrene should take account of the various resonance forms. There are four Kekulé forms of anthracene (not including the diagonal structure, which makes only minor contribution) and five of phenanthrene. Of these five, four have a double bond in the 9,10-position. One of the principal reactions of phenanthrene is addition to this double bond.

Reactions. Anthracene and phenanthrene undergo addition, substitution, and oxidation. They are reduced first to 9,10-dihydroanthracene and 9,10-dihydrophenanthrene, respectively (pp. 568, 569); hydrogenation leads to further reduction products. Oxidation yields the corresponding quinone. Because anthracene is the more readily oxidized by chromic acid or nitric acid, phenanthrene can be purified from anthracene by these reagents.

Halogens under controlled conditions first add: anthracene in carbon disulfide at 0° gives, with chlorine or bromine, 9,10-dichloro- or 9,10-dibromo-9,10-dihydroanthracene (anthracene dichloride or dibromide); phenanthrene in glacial acetic acid and bromine form 9,10-dibromo-9,10-dihydrophenanthrene (phenanthrene dibromide). These compounds are not very stable; when heated, hydrogen halide is evolved yielding 9-chloroanthracene, 9-bromoanthracene, or 9-bromophenanthrene. More halogen converts these to

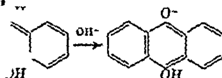


anthraquinone can be reduced to 9,10-dihydroxyanthra-
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Compounds

M.P. °C	B.P. °C
217	354–355
286	379–381
290	430
158–159	
341	
429–430	
262	
180	
101	340
206–207	>360
150	>360

solution is obtained. The reaction
Addition of acid to the blood-red

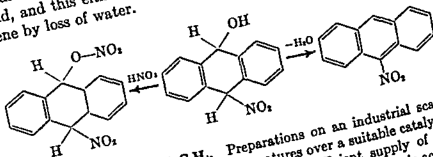


which places the negative charge on
oxygen of the air the reduced product is
itates from the solution with resultant
of reduction and oxidation form the basis
e derivatives of anthraquinone as dyes, so-
uced under alkaline conditions to form an
a fabric to be dyed is immersed. On
nerated and is precipitated as an insoluble

the 9,10-dihalo derivative or to other products. Phenanthrene and chlorine first yield 9,10-dichlorophenanthrene, then other products.

Sulfonation of anthracene at 100° with concentrated acid yields 1,5- and 1,8-anthracenedisulfonic acid, and at 120 to 135° with a somewhat dilute acid, 2-anthracenesulfonic and 2,6- and 2,7-anthracenedisulfonic acids. The β-monoacid is obtained best by heating anthracene and sodium bisulfate at 140°. Thus anthracene is seen to be easily sulfonated and to resemble naphthalene in yielding the α-acid at lower temperatures, the β-acid at higher temperatures. Phenanthrene on sulfonation with concentrated acid gives a mixture of 2-, 3-, and 9-phenanthrenesulfonic acids.

Nitric acid can yield addition as well as substitution products. The latter result under anhydrous conditions. Anhydrous nitric acid in glacial acetic containing acetic anhydride yields from anthracene, 9-nitroanthracene and 9,10-dinitroanthracene, and from phenanthrene a mixture of 9-, 2-, 4-, and 3-nitrophenanthrene (*ca.* 60, 20, 20, and 2%, respectively). Nitric acid (concd.) shaken with a suspension of anthracene in chloroform gives 9-nitro-9,10-dihydroanthranyl nitrate. The first product probably is an addition compound, and this either forms an ester with excess nitric acid, or 9-nitroanthracene by loss of water.



Anthraquinone, $C_6H_4(CO_2)_2C_6H_4$. Preparations on an industrial scale involve air oxidation of anthracene at elevated temperatures over a suitable catalyst, such as vanadium pentoxide. However, because of the insufficient supply of anthracene from coal tar, a more important method is through the benzoylbenzoic acid synthesis (pp. 531, 570). This is especially valuable for the preparation of substitution products, for example, 2-chloroanthraquinone, and is adaptable to either small scale or large scale operations.

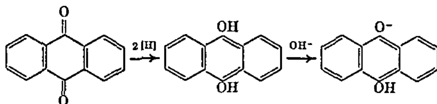
Anthraquinone is a yellow solid insoluble in water and only slightly soluble in the ordinary organic solvents, because of its high melting point (Table 96). It differs from p-benzoquinone in a number of respects: it has little odor, is not volatile with steam, is not reduced by sulfurous acid, does not add halogens, does not reduce ammoniacal silver solution, and is not easily oxidized. Some of these properties can be ascribed to its greater molecular weight, and thus lower vapor pressure, others to the fact that the reduction potential of anthraquinone is one of the lowest of quinones. It is significant that one can write four Kekulé resonance forms for anthraquinone, the same number as that for anthracene. This is not true of benzoquinone, or phenanthrenequinone; in these two cases the number of resonance forms of the hydrocarbon, and thus of the diol, exceeds by one those of the quinone. Thus there is less tendency for anthraquinone to be reduced to the diol. Reduction of anthraquinone to anthracene is described earlier (p. 568).

Under alkaline conditions anthraquinone can be reduced to 9,10-dihydroxyanthracene (anthrahydroquinone), analogous to reductions of other quinon s. A satisfactory reducing agent is either zinc dust or sodium dithionite, both with aqueous

TABLE 96 | Constants of Some Polynuclear Compounds

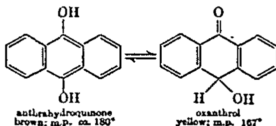
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1,2; 5,6-Dibenzanthracene	262	
20-Methylcholanthrene	180	
Phenanthrene	101	340
9,10-Phenanthrenequinone	206–207	>360
Pyrene	150	>360

sodium hydroxide. A deep blood-red colored solution is obtained. The reaction sometimes is used as a test for anthraquinone. Addition of acid to the blood-red solution causes anthrahydroquinone to precipitate.



The intense color is associated with resonance which places the negative charge on different carbon atoms. On exposure to oxygen of the air the reduced product is oxidized back to anthraquinone, which precipitates from the solution with resultant discharge of the red color. These reactions of reduction and oxidation form the basis of the use of highly colored water-insoluble derivatives of anthraquinone as dyes, so-called vat dyes. Such a compound is reduced under alkaline conditions to form an intensely colored solution (the "vat") in which a fabric to be dyed is immersed. On exposure to air the original compound is regenerated and is precipitated as an insoluble color within the fabric (Chap. 46).

Desmotropism. Anthrahydroquinone is the enolic form of a desmotropic (tautomeric; p. 326) pair, anthrahydroquinone ⇌ oxanthrol (called also oxanthrone)

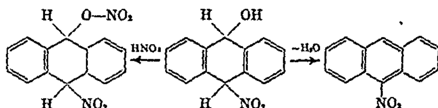


anthrahydroquinone brown; m.p. ca. 180°   oxanthrol yellow; m.p. 167°

the 9,10-dihalo derivative or to other products. Phenanthrene and chlorine first yield 9,10-dichlorophenanthrene, then other products.

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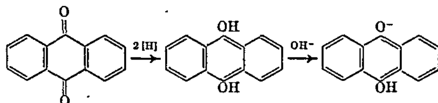
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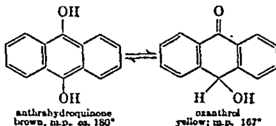
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anthrahydroquinone
brown, m.p. ca. 180°

oxanthrol
yellow; m.p. 167°

Each compound is known and is stable in solution. However, in alcoholic hydrogen chloride equilibrium is established; the equilibrium mixture is composed of 97 per cent anthrahydroquinone and 3 per cent oxanthrol.

Nitration and Sulfonation of Anthraquinone. Substitution reactions require strenuous conditions. Nitration with a mixture of anhydrous nitric and 100 per cent sulfuric acids at 125° yields mainly 1,5-dinitroanthraquinone, with smaller amounts of the 1,8-, 1,6-, and 1,7-dinitroanthraquinones. The most valuable of these derivatives is 1,5-dinitroanthraquinone, an intermediate in the manufacture of the vat dye, indanthrene yellow GK (Chap. 46).

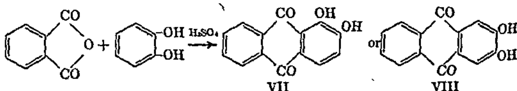
Sulfonation, the more important reaction, can be accomplished by heating with concentrated sulfuric acid at 250 to 260°, or with 40 to 45 per cent fuming sulfuric acid at 110 to 135°. The product is anthraquinone-2-sulfonic acid. If the reaction with fuming acid is carried out at 160°, other products are anthraquinone-2,6- and anthraquinone-2,7-disulfonic acid. These three sulfonic acids are used for the manufacture, by alkali fusion, of the three mordant type dyes, respectively, alizarin, flavopurpurin, and anthrapurpurin (p. 575).

Anthraquinone-1-sulfonic acid is formed to the extent of 80 per cent with fuming sulfuric acid at 100 to 135° in the presence of mercury salts. Without such salts the product would be the 2-sulfonic acid. In industry the two anthraquinonesulfonic acids are converted to 1-amino and 2-aminoanthraquinones, respectively, by autoclaving at 170 to 200° for many hours with aqueous ammonia containing other substances. These aminoanthraquinones are used in the preparation of various dyes (Chap. 46).

Alizarin, 1,2-Dihydroxyanthraquinone, $C_6H_4(CO)_2C_6H_2(OH)_2$. (Fr. *alizari*, madder root) This occurs in combination with glucose as the glucoside, ruberythric acid, in the root of the madder plant (*Rubia tinctorium*). Ruberythric acid undergoes hydrolysis, promoted either by the natural enzymes of the plant or by acid, yielding the red dye, alizarin, and the sugar, primaverose. The plant has been known from early times and has been used for the dyeing of fabrics since then. The colors obtained, usually reds or browns, depend upon the mordant used. The best known is "turkey red." Natural alizarin has been supplanted by synthetic alizarin. Alizarin was first isolated in 1826.

The first clue to the structure of alizarin was obtained in 1868 by Graebe and Liebermann, who obtained anthracene by distillation with zinc dust. They concluded that it is dihydroxyanthraquinone from the formula and a year later were able to isolate it from a reaction mixture obtained by fusion of dibromoanthraquinone with alkali. This was the first example of the synthesis of a naturally occurring dye stuff.

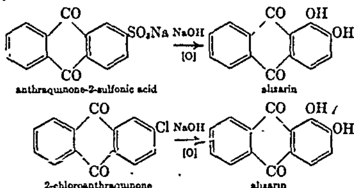
The structure of alizarin has been established by: (1) condensation of phthalic anhydride with pyrocatechol in the presence of sulfuric acid, and (2) nitration of alizarin. The first reaction gives two products, VII and VIII.



Nitration of alizarin yields two mononitro derivatives with the two nitro groups on the same benzene ring. This is the ring to which the two hydroxyl groups are attached. The unsubstituted ring, like the two benzene rings in anthraquinone, is not

easily nitrated. The formation of two mononitro derivatives shows that alizarin has structure VII. Structure VIII would yield only one mononitro derivative.

There are two important processes for alizarin synthesis: (1) fusion of anthraquinone-β-sulfonic acid with alkali containing an oxidizing agent, usually sodium chlorate, for oxidation at the α-position, and (2) fusion of 2-chloroanthraquinone similarly. Alizarin is obtained from the alkaline reaction mixture by adding acid. Anthracene is the starting point for the first synthesis, phthalic anhydride and chlorobenzene for the second (p. 531).



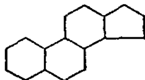
Alizarin can be formed in a number of other ways as, for example, when a mixture of phthalic anhydride and pyrocatechol is heated with sulfuric acid at temperatures ranging from 140 to 200°.

Other Anthraquinone Dyes. There are many other anthraquinone derivatives that are highly colored. A number of tri- and polyhydroxyanthraquinones are valuable mordant dyes. These must have two hydroxyl groups in the 1- and 2-positions. Purpurin is 1,2,4-, flavopurpurin is 1,2,6-, and anthrapurpurin is 1,2,7-trihydroxy-anthraquinone.

Vat dyes are neutral substances, highly colored, insoluble in water, and unaltered by light and air. Fabrics are impregnated with an alkaline solution of the reduced form (the vat). One of the simpler dyes of this type is Algol Red 5 G, 2,4-dibenzamido-9,10-anthraquinone (Chap. 46).

Phenanthrenequinone, Phenanthraquinone, $C_6H_4(CO)_2C_6H_4$. This is isomeric with anthraquinone and differs from it in having one direct attachment between benzene rings; another through two oxo groups (p. 569). It is oxidized by chromic anhydride or by potassium permanganate to diphenic acid and is reduced to phenanthrenehydroquinone (9,10-dihydroxyphenanthrene), a colorless solid, by heating with sulfurous acid in a sealed tube to 100°.

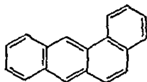
Sterols, Bile Acids, Sexual Hormones, and Cardiac-Active Principles. These important natural products have a carbon skeleton related to that of phenanthrene. They have, in addition to a reduced phenanthrene structure, a fused cyclopentane ring. The fundamental structure is that of perhydro-1,2-cyclopentenophenathrene, IX.



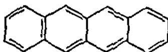
IX

The sterols and related compounds are often referred to as steroids.

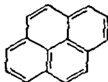
Polynuclear Hydrocarbons. These are often named from a hydrocarbon of fewer benzene nuclei, with the prefix, benzo- (or benz-). Thus phenanthrene can be called 1,2-benzonaphthalene and anthracene, 2,3-benzonaphthalene. The formulas of some of these more complicated hydrocarbons are shown.



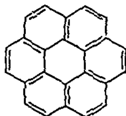
1,2-benzanthracene



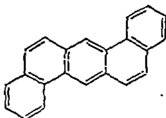
2,3-benzanthracene
naphthacene



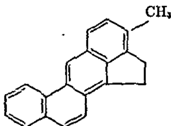
pyrene



coronene



1,2,5,6-dibenzanthracene



20-methylcholanthrene

Carcinogenic Hydrocarbons. It has been known for many years that the incidence of cancer among persons working in the coal-tar industry is higher than among the population as a whole. It has been found that quite a number of the more complex aromatic hydrocarbons, among them many present in coal tar, will initiate growth of skin tumors in susceptible strains of mice when the hydrocarbon remains in contact with the skin for some time. Among the coal-tar hydrocarbons possessing this property are 1,2-benzanthracene, pyrene, and 1,2;5,6-dibenzanthracene. It is rather significant that most of these are related to phenanthrene. One of the most active carcinogenic hydrocarbons is 20-methyl-cholanthrene. This hydrocarbon not only has a phenanthrene grouping, but also it has the carbon skeleton of the sexual hormones and related compounds. It has been suggested that certain steroids having a side chain properly located might be transformed in the body to methylcholanthrene. However, neither this nor related compounds have ever been isolated from cancer tissue.

PROBLEMS

1. Write the structures of the products to be expected by condensation of the following at 90 to 100° in a Friedel-Crafts reaction, followed by ring closure with hot sulfuric acid.

a) phthalic anhydride and toluene
b) phthalic anhydride and *m*-xylene
c) phthalic anhydride and bromobenzene
d) phthalic anhydride and *m*-dichlorobenzene
e) 3-chlorophthalic anhydride and toluene
f) 3-chlorophthalic anhydride and chlorobenzene

g) phthalic anhydride and *o*-dichlorobenzene
h) 3-bromophthalic anhydride and benzene
i) 3-bromophthalic anhydride and toluene
j) 4-bromophthalic anhydride and bromobenzene

2. Show how the following derivatives of phenanthrenequinone would be expected to be formed in an intramolecular benzoin condensation.

a) 3,6-dichloro
b) 3,6-dicyano
c) 3,6-dimethoxy
d) 2,7-dichloro
e) 1,8-dichloro
f) 1,8-dibromo
g) 2,3,6,7-tetrachloro

3. Show how the dialdehyde needed in Problem 2 may be synthesized from toluene.

4. Describe a convenient chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) anthracene and naphthalene
b) phenanthrene and naphthalene
c) 9,10-anthraquinone and 1,4-naphthoquinone
d) anthrahydroquinone and naphthahydroquinone
e) anthracene and 9,10-anthraquinone
f) anthracene and phenanthrene
g) 9,10-anthraquinone and 9,10-phenanthraquinone
h) 1,2-dihydroxyanthraquinone and 1,2-dihydroxyphenanthraquinone

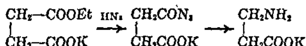
CHAPTER 40

Amino Acids

Amino acids have one or more amino groups and one or more carboxyl groups in the molecule. Aliphatic amino acids are of three main types, *viz.*, *alpha*, *beta*, and *gamma*. Of these the *alpha*-acids are by far the most important. Protein is built up from α-amino acids, either in large part, or entirely (Chap. 41). Amino acids can be named as amino substituents of the carboxylic acids, but the α-acids usually have their own trivial names. Most of these have the suffix -ine, *e.g.*, alanine.

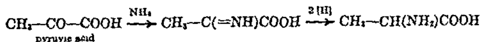
Preparation. The first, second, and fourth methods described below are general for the different types. The remaining ones are satisfactory for α-amino acids but usually not for others, because of other reactions.

1. *Degradation (Curtius) of half amides of dibasic acid.*

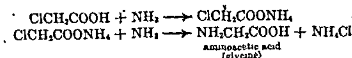


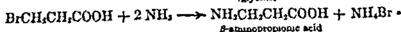
The reaction may involve an intermediate compound as a result of interaction of the intermediate isocyanate (p. 374) with the carboxyl group. Hydrolysis converts this finally to the desired product.

2. *Reduction of oxo acids in the presence of ammonia*, or reduction of the oxime or hydrazone of the oxo acid.

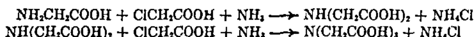


3. *Ammonolysis of halogenated acids.* The chloro derivatives of acetic and propionic acids may be used, but bromo derivatives of higher acids are better, because of low reactivity of the chloro compounds. The method is not satisfactory for β-amino acids because of the formation of unsaturated acids.



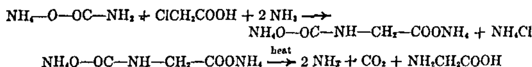


A complication is the formation of secondary and tertiary amino derivatives, *viz.,* dimethylamine-α,α'-dicarboxylic acid and trimethylamine-α,α',α''-tricarboxylic acid. In the case of aminoacetic acid these are formed so rapidly that with the proportions indicated only a few per cent of the desired product is obtained. It is necessary to use a very large excess of ammonia. With 60 moles a 70 per cent yield of glycine can be realized. However, side reactions are not so troublesome with α-bromo derivatives of butyric and higher acids.



$$NH_2CH_2COOH + ClCH_2COOH + NH_3 \longrightarrow NH(CH_2COOH)_2 + NH_4Cl$$
$$NH(CH_2COOH)_2 + ClCH_2COOH + NH_3 \longrightarrow N(CH_2COOH)_3 + NH_4Cl$$

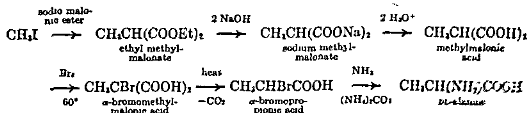
Addition of ammonium carbonate containing ammonium carbamate greatly improves the yield, so that, with chloroacetic acid, only 4 to 6 moles of ammonia are necessary.



$$NH_4{-}O{-}OC{-}NH_2 + ClCH_2COOH + 2\,NH_3 \longrightarrow NH_4O{-}OC{-}NH{-}CH_2{-}COONH_4 + NH_4Cl$$
$$NH_4O{-}OC{-}NH{-}CH_2{-}COONH_4 \xrightarrow{\text{heat}} 2\,NH_3 + CO_2 + NH_2CH_2COOH$$

The intermediate ammonium N-carboxycarbamate is unreactive towards chloroacetic acid; when heated, it slowly decomposes, by loss of ammonia and carbon dioxide, yielding glycine.

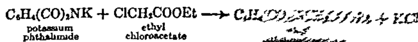
Ammonolysis of α-bromo acids is an important method of synthesis of higher α-amino acids. The steps are outlined for DL-alanine.



$$CH_3I \xrightarrow{\text{sodio malonic ester}} \underset{\text{ethyl methylmalonate}}{CH_3CH(COOEt)_2} \xrightarrow{2\,NaOH} \underset{\text{sodium methylmalonate}}{CH_3CH(COONa)_2} \xrightarrow{2\,H_3O^+} \underset{\text{methylmalonic acid}}{CH_3CH(COOH)_2}$$
$$\xrightarrow[60^\circ]{Br_2} \underset{\alpha\text{-bromomethylmalonic acid}}{CH_3CBr(COOH)_2} \xrightarrow[-CO_2]{\text{heat}} \underset{\alpha\text{-bromopropionic acid}}{CH_3CHBrCOOH} \xrightarrow[(NH_4)_2CO_3]{NH_3} \underset{\text{DL-alanine}}{CH_3CH(NH_2)COOH}$$

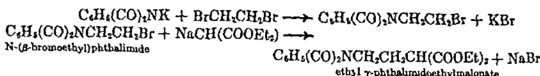
The advantages of this method are: (1) use of alkyl halides; (2) ease of bromination of the malonic acid, in comparison to that of the monocarboxylic acid; and (3) satisfactory overall yield. Benzyl chloride also may be used but not *p*-hydroxybenzyl chloride, because of the acidic nature of the phenolic function. However, the method can be applied to the synthesis of tyrosine, by starting with *p*-nitrobenzyl chloride and obtaining the hydroxyl group before carrying out the ammonolysis step.

4. *Gabriel synthesis.* For α-amino acids potassium phthalimide is heated to about 150° with an ester of an α-halogenated acid.

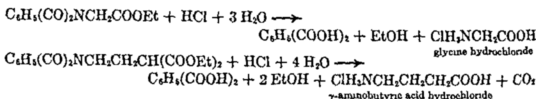


$$\underset{\text{potassium phthalimide}}{C_6H_4(CO)_2NK} + \underset{\text{ethyl chloroacetate}}{ClCH_2COOEt} \longrightarrow \underset{\text{ethyl phthalimidoacetate}}{C_6H_4(CO)_2NCH_2COOEt} + KCl$$

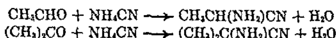
For other types, potassium phthalimide reacts first with an α,ω-dibromoalkane, and the product then reacts with sodio malonic ester.



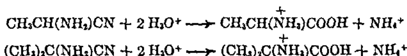
The phthalimide derivatives may be hydrolyzed in one operation with aqueous acid near 200° or in steps. In this case aqueous alkali readily opens the ring to form a derivative of phthalimidic acid, then acid hydrolysis completes the scission.



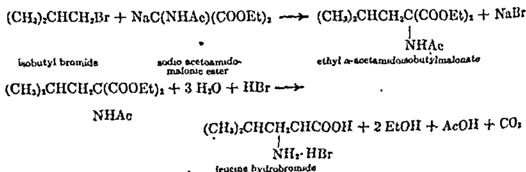
5. **Aminonitrile (Strecker) Synthesis.** This can be written as a reaction of ammonium cyanide with an aldehyde or ketone (p. 269).



As usually carried out, the oxo compound reacts first either with hydrogen cyanide to form a cyanohydrin or with ammonia to form an amino alcohol; then the intermediate reacts with either ammonia or hydrogen cyanide, respectively, to form the aminonitrite. This is hydrolyzed to the amino acid.

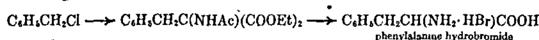


6. *Acetamidomalonic ester synthesis.* This ester is obtained from malonic ester (p. 331) through the steps: sodio malonic ester $\xrightarrow{BuONO}$ ethyl nitrosomalonate $\xrightarrow{H_2(Ni)}$ ethyl aminomalonate $\xrightarrow{Ac_2O}$ ethyl acetamidomalonate $\xrightarrow{NaOEt}$ sodio acetamidomalonic ester.



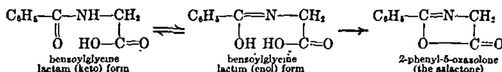
Ethyl acetamidomalonate is converted first to the sodium salt and this, by a reaction with an alkyl halide, produces a new carbon-to-carbon bond. Finally, hydrolysis with concentrated hydrobromic acid cleaves the ester and amide linkages, decarboxylation of the resulting malonic acid derivative fol-

lows, and the hydrobromide of a substituted glycine is the final product. This is one of the most useful syntheses for α-amino acids, because alkyl halides can be used. Also, in one operation the glycine unit is introduced into the molecule. Benzyl chloride also can be used, and the product has a benzene ring.

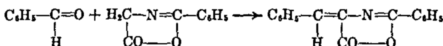


Hydroxybenzyl halides do not give good results, but the corresponding methyl ethers do, because the reactive phenol function is blocked; it finally is reformed during the last hydrolysis stage. Variations of this method (earlier ones) make use of ethyl phthalimidomalonate and ethyl benzamidomalonate.

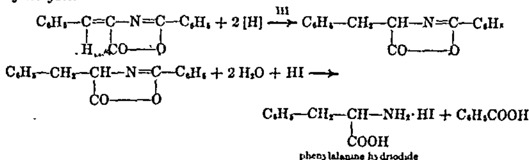
7. *Oxazolone (azlactone) synthesis.* Hippuric acid (benzoylglycine) reacts with an aldehyde at 100 to 130° in glacial acetic acid containing sodium acetate to produce a substituted 2-phenyl-5-oxazolone. The hippuric acid first goes over to its azlactone, probably by ring closure of its lactim form, and this, having a labile methylene group, is reactive towards aldehydes.



Sodium acetate is the basic catalyst as in the Perkin synthesis (p. 518). The reaction is more important for amino acids having an aromatic group. Benzaldehyde, for example, gives 2-phenyl-4-benzal-5-oxazolone.

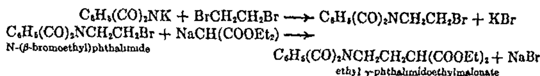


When this compound is heated with hydriodic acid and phosphorus, the olefinic double bond is reduced and the amide and imide linkages are cleaved by hydrolysis.

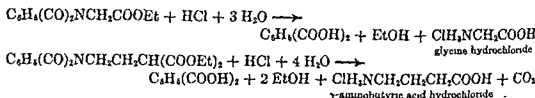


Hydroxybenzaldehydes give poor results, but if the hydroxy aldehyde is replaced by its methyl ether a good yield of the corresponding hydroxy amino acid is obtained. The ether is cleaved at the last hydrolysis step.

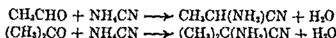
Obtaining the Free Amino Acid. In some cases, for example, method 3, the free amino acid is formed, but in others, methods 4, 5, 6, and 7, it is in the



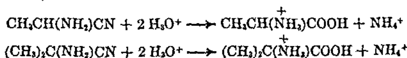
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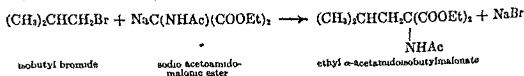
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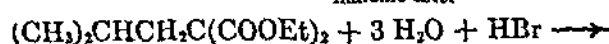


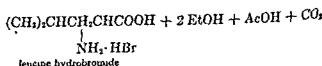
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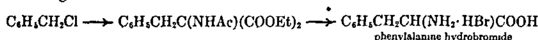






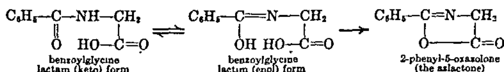
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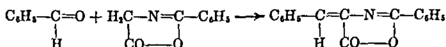


Hydroxybenzyl halides do not give good results, but the corresponding methyl ethers do, because the reactive phenol function is blocked; it finally is reformed during the last hydrolysis stage. Variations of this method (earlier ones) make use of ethyl phthalimidomalonate and ethyl benzamidomalonate.

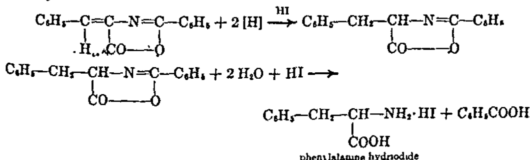
7. *Oxazolone (azlactone) synthesis.* Hippuric acid (benzoylglycine) reacts with an aldehyde at 100 to 130° in glacial acetic acid containing sodium acetate to produce a substituted 2-phenyl-5-oxazolone. The hippuric acid first goes over to its azlactone, probably by ring closure of its lactim form, and this, having a labile methylene group, is reactive towards aldehydes.



Sodium acetate is the basic catalyst as in the Perkin synthesis (p. 518). The reaction is more important for amino acids having an aromatic group. Benzaldehyde, for example, gives 2-phenyl-4-benzal-5-oxazolone.



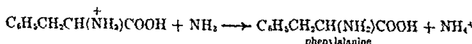
When this compound is heated with hydriodic acid and phosphorus, the olefinic double bond is reduced and the amide and imide linkages are cleaved by hydrolysis.



Hydroxybenzaldehydes give poor results, but if the hydroxy aldehyde is replaced by its methyl ether a good yield of the corresponding hydroxy amino acid is obtained. The ether is cleaved at the last hydrolysis step.

Obtaining the Free Amino Acid. In some cases, for example, method 3, the free amino acid is formed, but in others, methods 4, 5, 6, and 7, it is in the

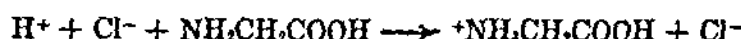
form of an ammonium salt. If the amino acid is slightly soluble in water, ammonia is added to the aqueous solution of the salt so as to bring it to the isoelectric point of the amino acid, as for example in the case of phenylalanine.



If the amino acid is water soluble, other methods must be adopted. In many cases, the amino acid can be precipitated as an insoluble copper salt and then can be recovered from this salt by removal of the copper, usually with hydrogen sulfide.

Reactions of Amino Acids. These are of two types, the ionic reactions of the amino and carboxyl groups, and the nonionic, typical organic reactions. Glycine is taken as an example.

1. *Basic properties.* Amino acids form stable salts with strong acids in aqueous solution. Salts with the hydrohalic acids usually are more soluble in water than the free acids.



2. *Acidic properties.* They form stable salts with strong bases. Those with sodium or potassium hydroxide often are more soluble in water than the free acids.



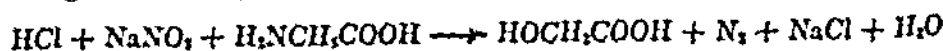
3. *Self-neutralization; dipolar ion structure.* The basic group can react with the acidic group. The product, an inner salt, has a dipolar ion structure (Ger. *zwitter ion*).



The dielectric constant of 2.5 *M* aqueous glycine is 137, while that of water is 80. This pronounced increase in the dielectric constant of the medium is regarded as evidence for the dipolar ion structure of glycine. The interpretation of the titration curve of glycine on the basis of the dipolar ion structure gives reasonable values for the basic and acidic constants (p. 592).

4. *Nonionic reactions of the amino group.* Aside from the reaction with nitrous acid, these take place when the carboxyl function is converted to an ester or amide function or, better, to a carboxylate ion function (characteristic of a sodium salt), because then the "blocking" of the carboxyl group allows the amino group to function normally.

a) *With nitrous acid.* This reaction is applied to the determination of free (not substituted) amino groups, usually by measurement of the volume of nitrogen evolved (Van Slyke method).



b) *Acylation.* A sodium salt can react in aqueous solution; an ester or amide can react in a nonaqueous solution, either with or without a tertiary amine (usually pyridine, Py).

$$(CH_3CO)_2O + \underset{\text{glycine anion}}{H_2NCH_2COO^-} \longrightarrow \underset{\text{acetylglycine}}{CH_3CONHCH_2COOH} + CH_3COO^-$$

$$Py + C_6H_5COCl + \underset{\text{ethyl aminoacetate}}{H_2NCH_2COOEt} \longrightarrow \underset{\text{ethyl benzamidoacetate}}{C_6H_5CONHCH_2COOEt} + Py \cdot HCl$$

$$Py + CH_3COCl + H_2NCH_2CONH_2 \longrightarrow \underset{\text{acetylglycylamide}}{CH_3CONHCH_2CONH_2} + Py \cdot HCl$$

$$\underset{\text{"carbobenzoxy" chloride}}{C_6H_5CH_2O{-}CO{-}Cl} + H_2NCH_2COO^- \longrightarrow \underset{\text{carbobenzoxyglycine}}{C_6H_5CH_2O{-}CO{-}NHCH_2COOH} + Cl^-$$

Even a very reactive acyl chloride, such as acetyl chloride, can be used with an aqueous solution of the salt by carrying on the reaction at 0° The "carbobenzoxy" derivatives are especially useful in the synthesis of peptides (p. 601). The chloride is prepared by the action of phosgene on benzyl alcohol.

$$\underset{\text{carbonyl chloride}}{ClCOCl} + \underset{\text{benzyl alcohol}}{C_6H_5CH_2OH} \longrightarrow \underset{\text{"carbobenzoxy" chloride}}{C_6H_5CH_2O{-}CO{-}Cl} + HCl$$

c) Formol titration. In the presence of formaldehyde a monoamino monocarboxylic acid can be titrated to a sharp endpoint with a strong base with phenolphthalein as indicator. An older explanation of this titration is the formation of a methylene derivative that blocks off the amino group. There are other explanations of the phenomenon. The endpoint lies on the basic side of neutrality where the C=N double bond is stable in water.

5. *Reactions of the carboxyl group.* These take place when the amino acid is in the form of a hydrohalic salt or of an acyl derivative because then the "blocking" of the amino group allows the carboxyl group to function normally.

a) Acyl halide formation. This is done usually with an inorganic acyl halide.

$$SOCl_2 + H_3\overset{+}{N}CH_2COOH \longrightarrow H_3\overset{+}{N}CH_2COCl + SO_2 + HCl$$

$$PCl_5 + CH_3CONHCH_2COOH \longrightarrow \underset{\text{acetylglycyl chloride}}{CH_3CONHCH_2COCl} + POCl_3 + HCl$$

$$PCl_5 + H_3\overset{+}{N}CH_2COO^- \xrightarrow{CH_3COCl} H_3\overset{+}{N}CH_2COCl + POCl_3 + Cl^-$$

This last method was much used by Emil Fischer in the synthesis of polypeptides.

b) Esterification. This is accomplished by adding alcohol to the hydrochloride of the amino acid chloride or by adding the amino acid to alcohol, passing in anhydrous hydrogen chloride until there is an excess and letting stand for some time. Reaction is faster with the acyl halide.

$$H_3\overset{+}{N}CH_2COCl + C_2H_5OH \longrightarrow H_3\overset{+}{N}CH_2COOC_2H_5 + HCl$$

$$H_3\overset{+}{N}CH_2COOH + C_2H_5OH \overset{HCl}{\rightleftharpoons} H_3\overset{+}{N}CH_2COOC_2H_5 + H_2O$$

$$Cl^- + H_3\overset{+}{N}CH_2COOC_2H_5 + EtONa \longrightarrow \underset{\substack{\text{ethyl aminoacetate}\\ \text{glycine ethyl ester}}}{H_2NCH_2COOC_2H_5} + EtOH + NaCl\downarrow$$

The ester can be recovered from the resulting hydrochloride on the addition of sodium ethoxide to the alcoholic solution.

Esters of acylated amino acids are readily prepared from the corresponding acyl halide and alcohol.

$$\underset{\text{acetylglycyl chloride}}{CH_3CONHCH_2COCl} + C_2H_5OH \longrightarrow \underset{\text{ethyl acetamidoacetate}}{CH_3CONHCH_2COOC_2H_5} + HCl$$

c) Amide formation at the carboxyl group. Reaction can be accomplished readily with an acyl halide.

$$\underset{\text{acetylglycyl chloride}}{CH_3CONHCH_2COCl} + 2\,NH_3 \longrightarrow \underset{\text{acetylglycylamide}}{CH_3CONHCH_2CONH_2} + NH_4Cl$$

It is thus possible to prepare a diamide of an amino acid. Application of these reactions to linking two or more amino acids is described in Chapter 41.

6 *Interactions of amino and carboxyl groups.* These two functional groups may react intramolecularly or intermolecularly, depending upon their relative positions. When heated, amino acids react in a manner resembling the hydroxy acids (p. 296). Esters may undergo similar reactions when heated, or even on standing.

a) α-Amino acids. Two molecules react. Glycine yields diketopiperazine, often called glycine anhydride. Alanine and higher acids yield substituted piperazines. The piperazine ring is described in Chapter 44.

$$2\,NH_2CH_2COOH \longrightarrow \underset{\text{diketopiperazine}}{\begin{array}{l} H{-}N{-}CH_2{-}C{=}O \\ \quad\;\; | \qquad\qquad\;\; | \\ O{=}C{-}CH_2{-}N{-}H \end{array}} + 2\,H_2O$$

$$2\,NH_2CH_2COOEt \longrightarrow \begin{array}{l} H{-}N{-}CH_2{-}C{=}O \\ \quad\;\; | \qquad\qquad\;\; | \\ O{=}C{-}CH_2{-}N{-}H \end{array} + 2\,EtOH$$

b) β-Amino acids. The usual reaction here is loss of ammonia, with formation of an unsaturated acid, rather than a reaction between the two functional groups.

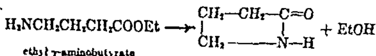
$$\underset{\beta\text{-aminopropionic acid}}{H_2NCH_2CH_2COOH} \longrightarrow \underset{\text{acrylic acid}}{CH_2{=}CHCOOH} + NH_3$$

The reaction is reversible, for β-amino acids have been prepared from α-unsaturated acids by heating with concentrated ammonium hydroxide under pressure.

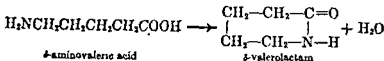
Cases are known, however, in which the two functional groups interact with formation of a β-lactam. (See next paragraph.) These are less common than γ- and δ-lactams and exist only when there are substituents on the α- and β-carbon atoms. Penicillin has a β-lactam group.

c) γ-Amino acids. These undergo an intramolecular reaction with formation of lactams.

$$\underset{\gamma\text{-aminobutyric acid}}{H_2NCH_2CH_2CH_2COOH} \longrightarrow \underset{\gamma\text{-butyrolactam}}{\begin{array}{l} CH_2{-}CH_2{-}C{=}O \\ | \qquad\qquad\quad\;\; | \\ CH_2{-}{-}{-}{-}{-}N{-}H \end{array}} + H_2O$$



d) δ-Amino acids. These also form lactams, but less readily than γ-acids. The main side reaction is an intermolecular one.

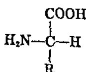


e) ε-Amino acids. With these and acids having an even greater separation of the two functional groups, intermolecular reactions are the rule. The products are linear polyamides of high molecular weight. The commercial development of such polyamides should lead to substances somewhat similar to nylon. The intermolecular reaction usually accompanies the main reaction of α-, β-, γ-, and δ-amino acids.

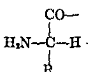
ALPHA AMINO ACIDS

Complex mixtures of these acids result from hydrolysis of proteins (Chap. 41). These hydrolyses are catalyzed by acids, bases, or proteolytic enzymes such as pepsin, trypsin, or papain. Alkaline hydrolysis has the disadvantage that optically active amino acids are liable to become racemised. There are three main types of these acids, *viz.*: *A*, monoamino monocarboxylic acids; *B*, diamino monocarboxylic acids; and *C*, monoamino dicarboxylic acids. Members of type *A* are essentially neutral, *B* are basic, and *C* are acidic amino acids. Type *A* includes hydroxy, sulfhydryl, pyrrolidine, aromatic, and heterocyclic amino acids.

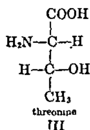
All of the α-amino acids from proteins with one exception are optically active, and belong to the L-family (p. 302). The exception is glycine. When the formulas are written with the carboxyl group at the top and projection is made in the recommended manner (p. 300), the α-amino group lies on the left, as shown by I. Some active amino acids are dextrorotatory, others levorotatory.



I



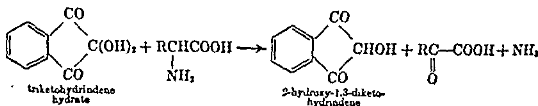
II



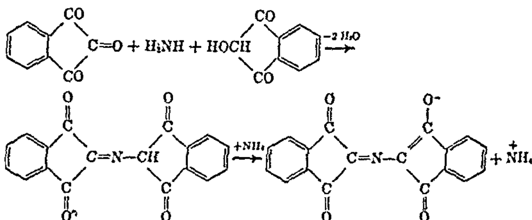
III

Amino acids from proteins usually are designated by their trivial names, for example, glycine, alanine, and tyrosine. The radicals, II, have corresponding names, for example, glycyl, alanyl, and tyrosyl. In the following descriptions of amino acids, reference to their presence in proteins means the radicals in combination, not the uncombined acids.

Ninhydrin test. All α-amino acids give an intense color (blue) when heated with a dilute aqueous solution of ninhydrin (triketohydrindene hydrate). This reagent removes ammonia from the amino acid by oxidation and is reduced to 2-hydroxy-1,3-diketohydrindene in the process.



Reaction then takes place between ammonia and the two hydrindene compounds, with formation of N-diketohydrindylidene-diketohydrindylamine.



This loses a proton to ammonia or some other base present and is converted into an intensely colored anion. The intense color is ascribed to the fact that the negative charge is distributed by resonance among the four oxygen and some of the carbon atoms (Chap. 46).

A. MONOAMINO MONOCARBOXYLIC ACIDS

Glycine, Glycocoll, Aminoacetic Acid, NH_2CH_2COOH. This is the simplest amino acid and differs from the others in being optically inactive. It has a sweet taste, hence the older name, glycocoll (Gr. *glykyl*, sweet + *kolla*, glue). Glycine is present in silk fibroin and in gelatin in relatively large amount and is a constituent of many other proteins. It is obtained by the hydrolysis of hippuric acid, benzoylglycine, $C_6H_5CONHCH_2COOH$, which occurs in the urine of horses. Feeding experiments have shown that the absence from the diet of glycine, combined or uncombined, does not lead to any physiologic disturbance. The organism is able to synthesize any needed glycine from other amino acids, consequently it is not an essential constituent of the diet, and it is not essential for normal growth. Many other amino acids are not essential. The essential ones are listed in Table 54 (p. 501).

L(+)-Alanine, α-Aminopropionic Acid, $CH_3CH(NH_2)COOH$. This is the simplest, optically active amino acid. Its best source is silk fibroin, of which it comprises 25 per cent. It is widely distributed among proteins.

L(+)-Valine, α-Aminoisovaleric Acid, $(CH_3)_2CHCH(NH_2)COOH$. This is present in small amounts in many proteins.

L(−)-Leucine, α-Aminoisocaproic Acid, $(CH_3)_2CHCH_2CH(NH_2)COOH$. This, along with isoleucine, is an important component of insulin, zein, edestin, and serum albumin. Leucine is widely distributed among proteins.

L(+)-Isoleucine, α-Amino-β-methylvaleric Acid, $CH_3CH_2CH(CH_3)CH(NH_2)$-COOH. This is isomeric with leucine but is not a true iso compound, since it lacks the typical isopropyl group at the end of a normal chain.

L(+)-Norleucine, α-Amino-n-caproic Acid, $CH_3(CH_2)_3CH(NH_2)COOH$. This is a minor constituent of proteins.

Hydroxyl Derivatives

L(−)-Serine, α-Amino-β-hydroxypropionic Acid, $HOCH_2CH(NH_2)COOH$. The principal source is silk (L. *sericus*) fibroin, from which it can be obtained by acid hydrolysis. Glyceric acid is formed from serine by the action of nitrous acid.

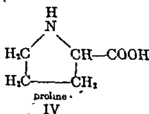
L(−)-Threonine, α-Amino-β-hydroxybutyric Acid, $CH_3CH(OH)CH(NH_2)$-COOH. This is present in small amount in some proteins. Casein has as much as 3.5 per cent. The molecule has two asymmetric carbon atoms. It is assigned to the L-family of amino acids on the basis of the configuration of the α-carbon atom, and to the D-family of hydroxy compounds, on the basis of the configuration of the β-carbon atom, III.

Sulfur Derivatives

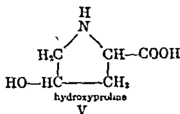
L(−)-Cystine, Bicystein, Bi-β-thiol-α-aminopropionic Acid, HOOCCH-$(NH_2)CH_2$—S—S—$CH_2CH(NH_2)COOH$. This and its reduction product, **L(−)-cysteine, β-thiol-α-aminopropionic acid, $HSCH_2CH(NH_2)COOH$,** are interrelated. Both may occur in proteins, but usually cystine is considered to be the more likely form. The oxidation-reduction system, cystine ⇌ cysteine is important in many biological oxidations. Cystine is more abundant in the harder types of proteins, such as hair, nails, horn, hoof, and feathers, than in other types. It is present in insulin.

L(−)-Methionine, α-Amino-γ-methylthiolbutyric Acid, $CH_3SCH_2CH_2CH$-$(NH_2)COOH$. This is present in many proteins, but is not as widely distributed as cystine.

Pyrrolidine Derivatives



proline
IV



hydroxyproline
V

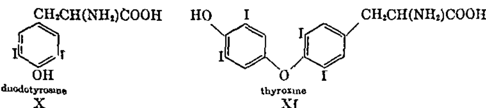
L(−)-Proline, 2-Carboxypyrrolidine, IV. This has been found in most proteins. The pyrrolidine ring (Chap. 44) of proline is a reduced pyrrole ring; the latter is important in connection with chlorophyll and hemoglobin (Chap. 44). Proline and hydroxyproline differ from other amino acids obtainable from proteins in having a secondary instead of a primary amino group. They are important components of gelatine (20 and 14%, respectively).

amide. Often some of the aspartic acid of protein is present as the amide, which may give rise to ammonia when the protein undergoes hydrolysis.

L(+)-Glutamic Acid, α-Aminoglutaric Acid, $HOOCCH_2CH_2CH(NH_2)COOH$. This is a constituent of most proteins. It is especially abundant in gliadin (44%), the principal protein of wheat. Gluten is the sticky, crude protein of wheat, obtained from a wheat flour dough by removal of most of the starch with a fine stream of water. Gluten contains also the protein glutenin. Glutamic acid often is present as the monoamide, **L(+)-glutamine**, $H_2NCOCH_2CH_2CH(NH_2)COOH$. This is especially true of the proteins of grains. When the protein is hydrolyzed, ammonia is formed by hydrolysis of the amide function. Glutamic acid is present in beet molasses. This is the main source of monosodium glutamate, which gives a meaty flavor and is extensively employed as a seasoning agent for meats, gravies, and soups. A trade name is Accent.

L(+)-Hydroxyglutamic Acid, α-Amino-β-hydroxyglutaric Acid, $HOOCCH_2CH(OH)CH(NH_2)COOH$. This is an important constituent of casein. It is found also in gliadin and in some other proteins.

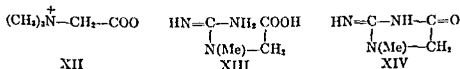
Rarer Amino Acids. Among those primarily of vegetable origin are **citrulline** and **3,4-dihydroxyphenylalanine**, and of animal origin, **L(+)-norvaline, L(+)-ornithine, L(+)-3,5-diiodotyrosine, thyroxine,** and **L-3,5-dibromotyrosine.** Citrulline, α-amino-δ-ureido-*n*-valeric acid, $(NH_2CONH)CH_2CH_2CH_2CH(NH_2)COOH$, is found in watermelon tissue. This acid has the urea residue in place of the δ-guanidino group of arginine. Dihydroxyphenylalanine has been found in bean seedlings and may be widely distributed. Norvaline, α-amino-*n*-valeric acid, $CH_3CH_2CH_2CH(NH_2)COOH$, is a minor constituent of a number of proteins. Ornithine, α,δ-diamino-*n*-valeric acid, $H_2N(CH_2)_3(NH_2)COOH$, is δ-amino-norvaline. It is obtained from arginine on hydrolysis.



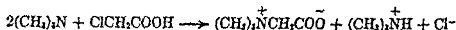
diiodotyrosine X   thyroxine XI

Diiodotyrosine, iodogorgoic acid, X, and thyroxine, XI, are found in the thyroid gland of mammals as a component of the protein, thyroglobulin. Iodogorgoic acid was first obtained by the hydrolysis of a species of coral (*Gorgonia cavolinii*). Thyroxine is not only a component of thyroglobulin but is present uncombined, to a slight extent. Thyroglobulin is the active principle of the thyroid gland. A deficiency of thyroxin may cause obesity, cretinism, retarded mental development, or other disturbance. Administration of extract of the thyroid gland or of synthetic thyroxin, usually orally, has been found to be beneficial. Dibromotyrosine has been isolated from the skeleton of *Primnoa lepadifera*.

Biologically Important Derivatives. Some of these are **betaine**, XII, **creatine**, XIII, and **creatinine**, XIV. Betaine is N,N,N-trimethylglycine, and is prepared by the reaction of trimethylamine and chloroacetic acid. It is a quaternary ammonium



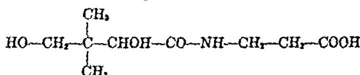
compound and must exist as a dipolar ion (inner salt). It occurs in sugar beets and



$$2(CH_3)_3N + ClCH_2COOH \longrightarrow (CH_3)_3\overset{+}{N}CH_2CO\overset{-}{O} + (CH_3)_3\overset{+}{N}H + Cl^-$$

can be obtained from beet sugar molasses. Creatine is N-methyl-N-guanidinoacetic acid. It occurs in muscle in combination with phosphoric acid as phosphocreatine. Creatinine is formed from creatine by loss of water when the latter is heated with dilute hydrochloric acid Creatinine is excreted in the urine. The two compounds are important in connection with muscular activity.

Pantothenic Acid, Vitamin B_3, (+)-α,γ-Dihydroxy-β,β-dimethylbutyryl-β'-alanide, $C_9H_{17}O_5N$. This occurs, usually in a form bound to protein, in all living substances (Gr. *pantothen*, from every side). It is believed that they require pantothenic acid for normal growth. Plants produce this substance after photosynthesis has started. The richest sources of pantothenic acid are liver and kidneys.



pantothenic acid

The vitamin has been synthesized by the condensation of α-hydroxy-β,β-dimethyl-γ-butyrolactone with β-aminopropionic acid (β-alanine).

TABLE 97 | **Constants of Some Amino Acids** [a]

NAME	$[\alpha]_D$ [b]	SOLY. IN H_2O AT 25° G./100 G.
Alanine	+14.47 [c]	16.51
Arginine	+27.58 [c]	
Aspartic acid	+24.62 [c]	0.500
Cystine	−212.9 [c]	1.096×10^{-2}
Duodotyrosine	+2.9 [c]	0.617
Glutamic acid	+31.71 [c]	0.843
Glycine		24.99
Histidine	−39.20	4.29
Hydroxyproline	−75.2	36.11
Isoleucine	+40.6 [c]	4.117
Leucine	+13.91 [c]	2.19
Lysine	+25.72 [c]	
Methionine	+23.4 [c]	3.381 [d]
Phenylalanine	−35.1	2.965
Proline	−85.0	162.3
Serine	+14.5 [c]	5.032 [d]
Threonine	−28.3	
Thyroxine	−4.4 [e]	
Tryptophane	−2.663	1.136
Tyrosine	−1.165 [c]	0.453
Valine	+1.93 [c]	8.85

[a] From M. S. Dunn and L. B. Rockland, *Advances in Protein Chemistry, III*, Academic Press, 1947, pp. 354 and 359.
[b] 20° or 25°. [c] Dil. HCl. [d] Value for DL-. [e] NaOH in EtOH.

Essential Amino Acids. The diet of humans must contain a number of amino acids for the maintenance of normal health and growth. The other acids can be synthesized by the body when the diet furnishes sufficient nitrogen. The essential amino acids, as determined by Rose and co-workers, are shown in Table 98. The results agree in general with earlier studies carried on with rats except that arginine and histidine are not essential for humans. However, arginine is necessary for activity of spermatozoa and has been designated by some as a paternity chemical.

TABLE 98 | **Essential Amino Acids**

NAME	MIN DAILY REQUIREMENT G	RECOMM DAILY INTAKE G.
L-Isoleucine	0.70	1 4
L-Leucine	1.10	2.2
L-Lysine	0 80	1 6
L-Methionine	1.10	2.2
L-Phenylalanine	1.10	2.2
L-Threonine	0.50	1.0
L-Tryptophane	0.25	0.5
L-Valine	0.80	1 6

From "Metabolism of Proteins and Amino Acids," by P. P. Swanson and H E. Clark, *Annual Review of Biochemistry,* Vol. 19, Annual Reviews, Inc., Stanford, Calif., 1950, p. 238.

Dissociation Constants of Amino Acids. These have been determined mainly from titration curves. The theoretical curve of glycine is shown in Figure 31. Curves of this type are obtained by measuring the pH of the solution as the titration is being carried out. In the case of glycine this is done usually by adding either an acid or a base to a solution of glycine. Or it can be done with a salt of glycine. It is noted that there are two main inflection points in Figure 31 at pH 2.4 and 9.8 respectively. Such an inflection point is obtained, in the titration of an acid, HA, by a base at the point of half neutralization. The pH at this point, because of the following relationship, is the pK_a of the acid.

$$K_a = \frac{[H^+][A^-]}{[HA]} = \frac{[H^+]y}{x - y}$$

Here the ionization constant of an acid, HA, is expressed in terms of the activities of the substances involved (activity is concentration times the activity coefficient). If the activity of all the acid is taken as x and that of the un-ionized form as y, then at the point of half neutralization, where $y = x/2$, the ionization constant, K_a, is equal to [H+], the activity of the hydrogen ion. Thus pH and pK_a are the same at this point, because pH is the negative logarithm of the hydrogen ion activity, and pK_a is the negative logarithm of K_a.

Starting at the upper left-hand corner with $NH_3^+CH_2COOH$, the positive glycine ion, addition of strong base removes a proton from one of the two

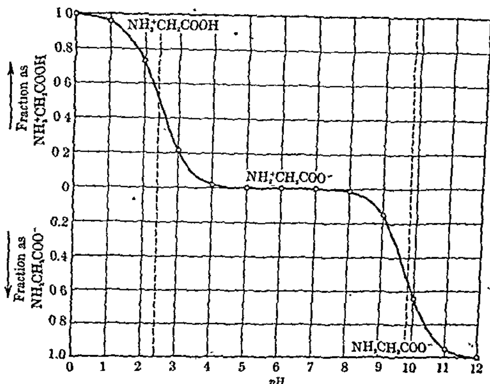
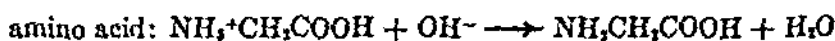
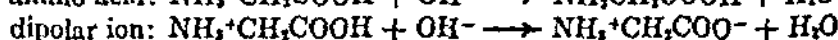


Figure 31 · Theoretical Titration Curve of Glycine

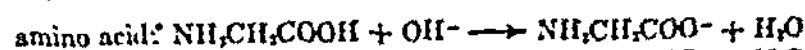
acidic groups, NH_3^+ or COOH, depending upon what the structure of glycine *is considered to be. The proton is removed from* NH_3^+ *if glycine has the* amino acid structure, and from COOH if it has the dipolar ion structure.

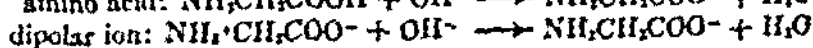

amino acid: $NH_3^+CH_2COOH + OH^- \longrightarrow NH_2CH_2COOH + H_2O$


dipolar ion: $NH_3^+CH_2COOH + OH^- \longrightarrow NH_3^+CH_2COO^- + H_2O$

The first inflection point, therefore, indicates that 2.4 is the pK_a of either NH_3^+ or COOH. If 2.4 is the pK_a of NH_3^+, then the basic strength of the NH_2 group is 11.6 (14 − 2.4). This is because K_a of NH_3^+, the conjugate acid of NH_2, and K_b of NH_2 are related to each other as $\log K_a + \log K_b = \log K_w$. *This is usually expressed as* $pK_a + pK_b = 14$, where pK_a is the negative log of K_a and pK_b is the negative log of K_b. Thus a value of 11.6 for pK_b of a base ($K_b = 10^{-11.6} = 4 \times 10^{-12}$) is too small for an aliphatic amine. On the other hand, a value of 2.4 for pK_a of a carboxyl group ($K_a = 2.5 \times 10^{-3}$) is a reasonable value for an acid.

The inflection point at pH 9.8 corresponds to reaction of either NH_2CH_2COOH or $\overset{+}{N}H_3CH_2CO\overset{-}{O}$.


amino acid: $NH_2CH_2COOH + OH^- \longrightarrow NH_2CH_2COO^- + H_2O$


dipolar ion: $NH_3^+CH_2COO^- + OH^- \longrightarrow NH_2CH_2COO^- + H_2O$

On the basis of the amino acid structure, 9.8 is pK_a of the COOH group ($K_a = 6.3 \times 10^{-10}$) an unreasonably small value, and on the basis of the dipolar ion structure it is pK_a of NH_3^+, or 3.2 for pK_b of the NH_2 group ($K_b = 1.6 \times 10^{-4}$), a reasonable value. Thus on the basis of the amino acid structure unreasonable values are obtained for the acid and base strengths, whereas reasonable values are obtained on the basis of the dipolar ion structure. It is customary to express the dissociation constants of amino acids, calculated from pH measurements, as pK_1', pK_2', etc., to indicate that they are **apparent dissociation constants.** True dissociation constants are calculated for infinite dilution. Values for the apparent dissociation constants of a number of amino acids are found in Table 99.

TABLE 99 **Dissociation Constants and Isoelectric Points of Amino Acids[a] at 25°**

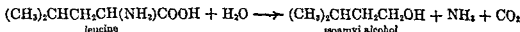
NAME	pK_1' COOH	pK_2' NH_3^+	pK_3'	pI'
Glycine	2.34	9.60		5 97
Alanine	2.34	9.69		6.00
Valine	2 32	9 62		5 96
Norvaline	2.36	9.72		6 04
Leucine	2 36	9.60		5.98
Isoleucine	2 36	9.68		6.02
Norleucine	2.39	9.76		6.08
Serine	2.21	9.15		5 68
Threonine	2.55	9.60		6.08
Cysteine	1.96	8 18	10 28(SH)	5 07
Methionine	2.28	9.21		5 74
Proline	1.99	10.60		6.30
Hydroxyproline	1.92	9.73		5 83
Phenylalanine	1.83	9 13		5 48
Tyrosine	2.20	9.11	10.07(OH)	5 66
Tryptophane	2 38	9 39		5 89
Histidine	1.82	6 00(Im.)	9.17(NH_3^+)	7 59
Arginine	2.17	9.04(NH_3^+)	12.48(Guan.)	10.76
Lysine	2.18	8.95(αNH_3^+)	10.53(ϵNH_3^+)	9.74
Aspartic acid	1 88	3 65(COOH)	9.60(NH_3^+)	2.77
Glutamic acid	2.19	4.25(COOH)	9.67(NH_3^+)	3 22
Hydroxyglutamic acid	2 33	4 24(COOH)	9.56(NH_3^+)	3.29

[a] From *Proteins, Amino Acids, and Peptides,* by E. J. Cohn and J. T. Edsall, Reinhold Publishing Co., New York, 1943, pp. 84 and 85.

Isoelectric Point. The isoelectric point of an amino acid is defined as the hydrogen-ion activity of the solution in which the amino acid does not migrate under the influence of an electric field. Under these conditions the concentration of positive amino acid ion is equal to the concentration of negative amino acid ion. This is usually the condition of minimum solubility

of the amino acid in water. The isoelectric point of a monoamino monocarboxylic acid, usually expressed as pI', can be calculated from the respective dissociation constants, according to the expression: $pI' = \frac{1}{2}(pK_1' + pK_2')$.

Amino Acids and Fusel Oil. During alcoholic fermentation of maltose produced from starches (p. 642), some of the amino acids in the grain proteins are converted to alcohols by the yeast, which can then make use of the nitrogen for its growth. A typical reaction taking place is the conversion of leucine to isoamyl alcohol, the principal constituent of fusel oil.



$$\underset{\text{leucine}}{(CH_3)_2CHCH_2CH(NH_2)COOH} + H_2O \longrightarrow \underset{\text{isoamyl alcohol}}{(CH_3)_2CHCH_2CH_2OH} + NH_3 + CO_2$$

PROBLEMS

1. Show the steps of a convenient synthetic method for the following, starting with a halogen compound of two less carbon atoms, and making use of ammonolysis of a halogen compound, to introduce the amino group.

a) DL-α-amino-n-butyric acid
b) DL-valine
c) DL-norvaline
d) DL-leucine
e) DL-isoleucine
f) DL-norleucine
g) DL-phenylalanine
h) DL-methionine
i) DL-ornithine
j) DL-aspartic acid

2. Ditto, but making use of acetamidomalonic ester, instead of ammonolysis of a halogen compound.

a) DL-alanine
b) DL-valine
c) DL-norvaline
d) DL-leucine
e) DL-isoleucine
f) DL-norleucine
g) DL-methionine
h) DL-phenylalanine
i) DL-ornithine
j) DL-aspartic acid

3. Show how the following may be prepared by the Strecker synthesis, starting with an alcohol or acid of one less carbon atom, whichever is better.

a) DL-alanine
b) DL-valine
c) DL-norvaline
d) DL-leucine
e) DL-isoleucine
f) DL-norleucine
g) DL-phenylalanine
h) DL-tyrosine

4. Starting with toluene as the only aromatic compound, show steps for a practical synthesis of the following DL-compound.

a) β-phenylalanyl amide
b) β-phenylalanyl-p-toluidide
c) N-acetyl-β-phenylalanine
d) N-benzoyl-β-phenylalanine
e) tyrosyl amide
f) tyrosyl-N-ethylamide
g) tyrosyl-N,N-dimethylamide
h) N-benzoyltyrosine
i) N-carbobenzoxy-β-phenylalanyl-o-toluidide
j) N-carbobenzoxytyrosine
k) p-acetoxy-β-phenylalanine

l) ethyl α-amino-β-phenylpropionate
m) methyl α-benzamido-β-phenylpropionate
n) benzyl α-acetamido-β-phenylpropionate

5. Describe a chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) alanine and alanyl-N-methylamide
b) alanine and alanine ethyl ester
c) alanine and N-acetylalanine
d) alanine and N-benzoylalanine
e) alanine and N-carbobenzoxyalanine
f) methionine and N-benzenesulfonylmethionine
g) alanine and tyrosine
h) alanine and tryptophane
i) tyrosine and tyrosine methyl ester
j) tyrosine and tyrosyl-N-ethylamide
k) tyrosine and N-acetyltyrosine
l) tyrosine and N-benzoyltyrosine
m) tyrosine and N-carbobenzoxytyrosine
n) tyrosine and α-N-acetyltyrosylamide

6. Write the structure of the amino acid that gives rise during yeast fermentation to:

a) *n*-propyl alcohol
b) *n*-butyl alcohol
c) isobutyl alcohol
d) active amyl alcohol

7. Show how to derive the expression for the isoelectric point from pK_1' and pK_2' of a monoaminomonocarboxylic acid.

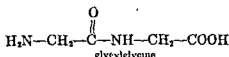
8. Compound *A*, $C_{11}H_{13}O_3N$, is almost insoluble in water and in cold dilute aqueous acids, soluble in cold dilute aqueous sodium hydroxide. On boiling for some time with constant boiling hydrochloric acid, *A* slowly dissolves. When the resulting solution is made neutral with ammonium hydroxide, compound *B*, β-phenylalanine, separates. What deductions can be drawn from these statements? Show how they lead to a structure for *A*.

CHAPTER 41

Proteins

Proteins are nitrogenous substances of plant and animal origin which have large molecular weights. They are of great importance because they are constituents of all living cells and are essential to life processes. In plants their greatest concentration is found in seeds. In animals they constitute the structural features, such as skin, nails, muscle, tendons, and organs; they contribute materially to the structure of bones, which contain also much calcium phosphate.

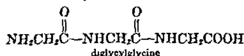
Proteins are composed mainly of α-amino acids (see Classification, p. 604). The attachment of one amino acid to another is by an amide linkage between the α-amino group of one molecule and a carboxyl group of the other (in dibasic acids, the one next to the amino group). The simplest compound of this type would be the one between two molecules of glycine, *viz.*, glycylglycine.



glycylglycine

A compound resulting from two molecules of amino acid (or acids) is called a dipeptide, from three molecules, a tripeptide, and so on. Usually they are referred to as polypeptides, or merely as peptides.

In tripeptides, one amino acid residue is attached to two others, one at the nitrogen atom of the original amino group, the other at the carbon atom of the original carboxyl group. The simplest compound of this type is diglycylglycine.



diglycylglycine

In tetrapeptides there are two such bivalent residues, and so on. The amide bond is called a peptide bond. A large number of amino acids can be attached so as to form a long chain, called a peptide chain. In this there is a repetition of —NHCHRCO— groups, where R is the group attached to the glycine unit.

In protein molecules there are a large number of amino acid molecules in combination. All of these, with the exception of glycine, have the L-configuration (p. 585). *In salmine, one of the smallest of the proteins, with* molecular weight of 7870 (Table 100) there are 58 amino acid residues per molecule. These can be combined in a very large number of ways. These actually are relatively few, in comparison to other proteins of about the same molecular weight, because of the relatively few amino acids present and the high abundance of one amino acid, *viz.*, arginine, 85.2 per cent, in salmine. With a larger number of amino acids and/or higher molecular weight, the possible different sequences of amino acid residues becomes very large

The complete structure of the molecule of a given simple protein (p. 694) would be determined if the following facts were known: (1) the kind of units of which it is composed; (2) the number of these; (3) the sequence of attachment: and (4) the spatial arrangement of the peptide chain. Purification and chemical analysis (Table 100) have been so perfected that the amino acid content is being well established for many proteins. From molecular weight determinations it is possible to calculate the approximate number of amino acid residues per molecule. From the nature of partial degradation products it is possible to obtain some idea of the sequence of amino acids, and from X-ray analysis the arrangement of the amino acids in space has been determined for some proteins.

A large number of investigators are actively at work on different aspects of protein structure. Much progress is being made on this, the most important of the unsolved problems of organic chemistry.

Physical Properties of Proteins. Proteins are solids without definite melting points. Decomposition takes place before melting. Solubilities vary, as mentioned under Classification. Solubilities are a minimum at the isoelectric points. Most proteins will not pass through semipermeable membranes.

Proteins are purified by slow crystallization from solutions at controlled *p*H. Electrophoresis is another method of purification. In this a protein, in solution at a definite *p*H, is caused to migrate in an electric field.

Protein is said to be denatured when, by the action of heat or by the addition of a number of substances, for example, alcohol, dilute acid, dilute alkali, or urea, it is changed to a form that is insoluble at its isoelectric point. The change takes place without the splitting of any amide or peptide bonds. The process of denaturation is explained as the result of a modification of the spatial arrangement of the amino acid residues in the long chain of the protein molecule. The denaturation process has been reversed.

Reactions of Proteins. There are a number of color tests for proteins, the most important of which are given below.

1. *Biuret reaction.* Addition of a small amount of copper sulfate to an alkaline solution of a protein or a protein hydrolysate gives a blue-violet to pink color, the former color with the longer protein chains, the latter with the shorter ones.

2. *Lead sulfide test.* Boiling a protein with aqueous sodium plumbite gives a black precipitate of lead sulfide, in case cystine or cysteine is a component.

3. *Ninhydrin reaction.* Proteins and their hydrolysis products, like the α-amino acids, give a color when heated with a solution of ninhydrin (p. 586); colors range from a blue to a violet-pink, or even red.

4. *Millon's test.* Heating proteins with a solution of mercurous nitrate containing nitrous acid or oxides of nitrogen produces a red color. This test is due to the presence of tyrosine.

5. *Xanthoproteic test.* Addition of nitric acid to a protein gives a yellow color, intensified to orange when made basic by sodium or ammonium hydroxide. This is characteristic of tyrosine and tryptophane (p. 588).

Hydrolysis of Proteins. This can be accomplished by heating with aqueous acids or bases, or by the action of enzymes, for example, pepsin, trypsin, [illegible] of causing consider- [illegible] o cause destruction, as by decarboxylation or deamination. Sometimes acid hydrolysis causes racemization with prolonged heating. Hydrolysis is the most important reaction, because through it not only are the various amino acids made available to living cells, but also the scientist can learn the kind of amino acids present in a given protein and the order in which they are built into the protein molecule.

In the body the various enzymes bring about cleavage of certain peptide bonds, with formation of smaller and smaller groups, finally even individual amino acids. When the groups are small enough to pass through the intestinal walls they enter the blood stream and are transported to various parts of the body where they are taken up by different cells, as needed.

The first comprehensive attack on protein structure was that of Emil Fischer, who subjected a number of proteins to hydrolysis by concentrated hydrochloric acid. The amino acids were converted into ethyl esters and these were subjected to distillation under reduced pressure. The esters of the monoamino monocarboxylic acids are more volatile than those of acidic or basic amino acids, and also they can be partially separated from one another by such distillation. There is much loss in this method.

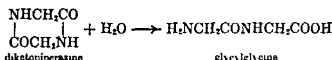
Following Fischer's earlier work there have been numerous improvements in methods of separating and analyzing for the various amino acids. Dakin developed the method of continuous extraction of an aqueous solution of amino acids with 1-butanol. This removes the neutral amino acids, leaving behind diamino acids and dicarboxylic acids. In order to obtain a solution of amino acids only, hydrolysis of the proteins was carried out with 30 per cent sulfuric acid, which later was removed with barium hydroxide, before extraction was started. The recovery of amino acids by this method is very good; 91.3 per cent in the case of gelatin, 100 per cent in the case of zein.

Among the most important of the newer methods developed for amino acid analysis are the use of specific precipitants for individual acids, isotopic dilution, and chromatography, in particular, partition chromatography. This

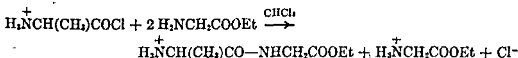
last is being used with marked success for the separation, identification, and determination not only of the individual acids but also of dipeptides and even more complicated molecules. In the isotopic dilution method, the amino acids of a protein hydrolysate are converted to derivatives by means of a reagent that has a radioactive element, for example, *p*-iodobenzenesulfonyl chloride. This, containing some radioactive iodine or sulfur, gives radioactive derivatives of the amino acids. Excess of reagent is removed. Then a very large excess of the derivative of a particular amino acid, but not radioactive, is added in known amount to the mixture of active derivatives. The derivative in question is then separated and purified to constant radioactivity. From the amount recovered and its radioactivity the weight of amino acid in the hydrolysate can be calculated. This has developed into one of the most accurate methods, with an error of 1 to 2 per cent. The amino acid recoveries from a number of proteins are shown in Table 100 (p. 600).

Synthesis of Peptides. Methods of synthesis of peptides are related to the reactions of amino acids (Chap. 40). Of the methods described here, the first three were developed by E. Fischer.

1. *Mild acid hydrolysis of diketopiperazines* (p. 584). This reaction is especially useful for the preparation of glycylglycine.



2. *Reaction of the hydrochloride of the acyl chloride of one acid* (p 583) *and the ester of a second.*



The dipeptide ester salt is converted to the free dipeptide as described under the next heading. This can be converted into the hydrochloride of the peptide acyl halide with acetyl chloride and phosphorus pentachloride (p. 583), and the product used for the synthesis of a tripeptide. This method can be used with optically active acids.

3. *Reaction of α-chloro(bromo)acyl chlorides with salts or esters of amino acids or peptides.*

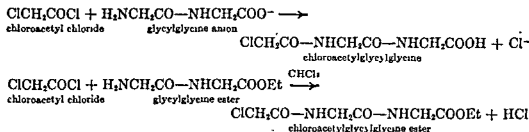
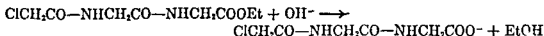


TABLE 100 | *Amino Acids from Some Proteins*

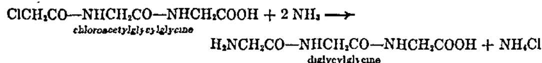
	MOL. WT.	SALMINE %	EDESTIN %	HEMOGLOBIN (HORSE) %	INSULIN %	β-LACTOGLOBULIN %	OVALBUMIN %	FIBRINOGEN %	GLIADIN %	KERATIN (WOOL) %	MYOSIN %	ZEIN %
Glycine	75 07	2 94	—	5.60	4.3	1.50	3 05	5.6	—	6.51	1 9	—
Alanine	89 09	1.12	4.31	7.40	4 5	6.42	6.72	3.7	2.13	4.14	6.5	10.5
Valine	117.15	3.14	5.7	9.10	7.75	5.72	7.05	4.1	2 66	4.64	2.6	3.52
Leucine	131.17	1.64	4.7	15 40	13 2	15.46	9.2	7.1	11.90	11.3	15.6	22.5
Isoleucine	131.17		7.5	0	2 77	5.90	7.0	4 8				
Phenylalanine	165 19		5.45	7.70	8.14	3.95	7.66	4 6	6.44	3.65	4.3	5.91
Tyrosine	181.19		4.34	3 03	13.03	3 73	3.68	5.5	3 2	4.65	3.4	5.25
Tryptophane	204 22		1.48	1.70	—	1.90	1.20	3.3	0.6	1.80	0.8	0.12
Serine	105 09	9 1	6.3	5 8	5.23	4.07	8.15	7 0	4.9	10.01	4.33	7.05
Threonine	119.12		3.85	4 36	2 08	5.15	4.03	6.10	2.1	6.42	5.11	3.45
Cystine (half)	240 29		0.93	0 45	12.5	2.29	0.51	2.3	2.50	11.88	1.4	0.83
Cysteine	121.16		0 50	4.64	—	1.10	1.35	0 4				
Methionine	149.12		2 4	1.0	—	3 20	5.20	2.6	1.69	0.7	3.4	2.41
Proline	115 08	5 80	4.25	3.9	2.53	5.4	3 60	5.7	13.35	9.5	1.9	10.53
Arginine	174.20	85.2	16.7	3 65	3.07	2.86	5.72	7.8	2.74	10.39	7.36	1.71
Histidine	155.16		2 9	8.71	4.91	1.58	2.35	2.6	1.82	1.05	2.41	1.32
Lysine	146.19		2.4	8.51	2.51	11.30	6.30	9.2	0.65	2.76	11.92	0
Aspartic acid	133 10		12.0	10 6	6.8	11.40	9.30	13.1	-1.34	6.57	8 9	4.61
Glutamic acid	147.13		20.7	8.5	18.60	21.50	16.50	14 5	45.7	14.7	22 1	26.9
Amide N.			2.15	1.1	1.69	1.30	1.23	—	5 45	1.42	1.45	3.61
Total N.			18 55	16.8	15.54	15.60	15.76					
Total (not incl. total N)		108.94	108.5	106.87	113.60	115.73	109.8	110.0	103.8	111 5	103.96	106.61
Per cent of total protein N		99.92	94	97.3	97.8	98	96.8					

From "Amino Acid Composition of Purified Proteins," by G. R. Tristam, *Advances in Protein Chemistry V*, Academic Press, New York, 1949.

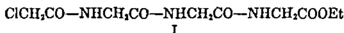
The ester is saponified very easily with 1 *M* base and goes into solution. The acid is precipitated on the addition of a strong acid.



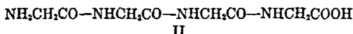
The chloro derivative obtained either way may be converted into a tripeptide by the action of liquid ammonia at room temperature for some days or by standing for some time in aqueous ammonia.



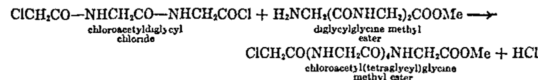
Chloroacetylglycylglycine can be converted to an acyl halide and this can react with a salt of another molecule of amino acid or peptide. The product, on ammonolysis, yields a tetrapeptide or higher peptide. Or, diglycylglycine can be converted to the ethyl ester with ethanol and hydrogen chloride, and this with chloroacetyl chloride yields chloroacetyl(diglycyl)glycine ester, I.



By saponification first, followed by ammonolysis, this is converted into triglycylglycine, II.



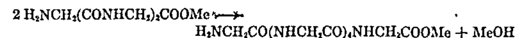
Chloroacetyldiglycyl chloride, instead of reacting with a salt of glycine, can react with a diglycylglycine ester.



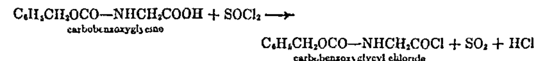
The product chloroacetyl(tetraglycyl)glycine ester, on saponification and ammonolysis, would yield the hexapeptide, pentaglycylglycine.

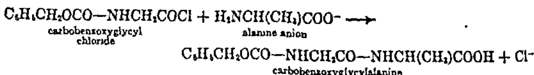


An ester of the hexapeptide can be formed also by heating diglycylglycine methyl ester.

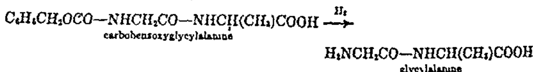


4 *Reaction of "carbobenzoxy" derivatives.* The amino group is protected first, and then a sequence of reactions carried out.





The "carbobenzoxy" group is removed by hydrogenolysis (H_2 with a catalyst, or Na and liquid ammonia).



A tripeptide can be made by changing the carbobenzoxy dipeptide to the acid chloride and having this react with another amino acid anion. The advantage of this method is easy removal of the protecting group by *reduction*, without affecting the other amide linkages.

Complex polypeptides have been synthesized. Fischer and co-workers in 1907 obtained the octadecapeptide, leucyl(triglycyl)leucyl(triglycyl)-leucyl(octaglycyl)glycine by method 3, starting with diglycylglycine and pentaglycylglycine. The former was combined with optically active (+)-α-bromoisocaproyl chloride to yield α-bromoisocaproyl(diglycyl)glycine, and this with phosphorus pentachloride and acetyl chloride gave the acid chloride, α-bromoisocaproyl(diglycyl)glycyl chloride. This with pentaglycylglycine gave α-bromoisocaproyl(octaglycyl)glycine and by ammonolysis this was converted to an active decapeptide, L-leucyl(octaglycyl)glycine.



The decapeptide under alkaline conditions reacted with α-bromoisocaproyl-(diglycyl)glycine to give a bromo compound that was converted to a tetradecapeptide with ammonia



A repetition of the reactions yielded an optically active octadecapeptide



This had a molecular weight of 1213. Later Abderhalden and Fodor prepared a nonadecapeptide, leucyl(triglycyl)leucyl(triglycyl)leucyl(triglycyl)leucyl-(pentaglycyl)glycine, having a molecular weight of 1326. Each of these compounds, at the time of its synthesis, had the greatest molecular weight among compounds of known structure.

These polypeptides were amorphous solids giving the biuret test. T were moderately soluble in cold water; when dissolved in warm water clear filtered solutions became opalescent in the cold. Addition mon sulfate caused separation from solution. In these respects resemblance to certain of the proteins.

between chains may in some cases be the result mainly of hydrogen bonding, in other cases of chemical bonding, as through the sulfur atoms of cystine (keratin) or through free amino and carboxyl groups. Typical fibrous proteins are fibrinogen (blood plasma), myosin (muscle), tobacco mosaic virus, and keratin (hair, wool). Collagen has a fibrous structure but here the chains are interconnected at frequent intervals, producing a network.

In other proteins the peptide chain is folded, instead of extended. This may give a fairly symmetrical globular structure, somewhat spherical in shape, for example, ovalbumin and β-globulin (blood plasma), or a less symmetrical molecule, intermediate in shape between the globular and fibrous molecules.

Classification of Proteins. Classification cannot be made on the basis of structure because at the present time the complete structures of proteins are not known, although much is known about the amino acid content, molecular shape and size, sp tial arrangement in the peptide chain, and sequence of attachment. In 1908 the American Physiological Society and the American Society of Biological Chemists adopted a classification, based in part on composition and in part on solubility, into simple proteins, conjugated proteins, and derived proteins. This classification has been followed in a general way but is modified and amplified.

Simple Proteins. These yield only α-amino acids on hydrolysis. The division of this group is made mainly on the basis of solubility.

1. **Albumins.** These are soluble in water, in dilute aqueous acid or base, or in dilute salt solutions. They are not precipitated from solution by ammonium sulfate until the salt concentration is above 2 *M*. They are coagulated by heat. Examples: *lactalbumin* (milk); *ovalbumin* (egg white); *serum albumin* (blood serum).

2. **Globulins.** These are insoluble in water at their isoelectric points. They dissolve in dilute aqueous acid or base, or in dilute salt solutions. *Addition of ammonium sulfate to about 2 M* causes precipitation of globulins at different salt concentrations. This group sometimes is divided further into **euglobulins,** as just defined, and **pseudoglobulins,** soluble in pure water. Globulins are widely distributed in seeds. Examples: *fibrinogen* (blood serum); *serum globulins* (blood serum, including antibodies); *edestin* (hemp seed); *legumin* (peas).

3. **Glutelins.** These are insoluble in all neutral solvents at their isoelectric points, soluble in dilute aqueous acid or base Unlike globulins, they do not dissolve in salt solutions. . They appear t[illegible] of proteins. occur mainly in seeds. Examples: *glutenin* [illegible] *an* (barle[illegible] *zenin* (rice).

4. **Prolamins.** These are globulinlike pr[illegible] seed ori[illegible] soluble in water, soluble in aqueous alc[illegible] [illegible]tively amounts of proline on hydroly[illegible] e the [illegible] gl[illegible] acid content but are not ac[illegible] becau[illegible] free but are in the amide for[illegible] n 58[illegible] (rye); *hordein* (barley); *zein* [illegible]

stance. A number of secretions, *i.e.*, saliva, gastric juice, and intestinal juice, contain *mucins*, the prosthetic group of which is a hexuronic acid (p. 633).

3. **Lipoproteins.** The prosthetic group is a phospholipid (p. 366). These proteins are present in the blood plasma.

4. **Nucleoproteins.** In these a protein is combined with a nucleic acid (Chap. 45), the prosthetic group. Nucleoproteins occur in all living cells and are very important biologically. Also, they are present in bacteria and viruses.

5. **Phosphoproteins.** In these there are phosphoric acid residues that are attached, through ester linkages, to the hydroxyl groups of serine molecules The best known example is *casein*, the principal protein of milk. Another is *vitellin*, in egg yolk.

Derived Proteins. This group includes the various products resulting from proteins by some physical agency, such as heat, or by some chemical agent, such as acid, base, enzyme, or alcohol. The first change that takes place is denaturation, next, degradation. This, under the influence of acids, bases, or enzymes, may lead finally to amino acids. A number of names have been used to indicate various intermediate products of hydrolysis, such as *proteoses*, *peptones*, and *peptides*, in general, of decreasing order of complexity.

Enzymes, Hormones, Antibodies, and Viruses. Since these are distributed among the various classes of proteins, it seems better to describe them separately.

Enzymes appear to be conjugated proteins, in the main. They are classified on the basis of the types of reactions they promote, for example, *hydrolysases* (causing hydrolysis), *decarboxylases* (loss of carbon dioxide), and those promoting oxidoreductions. Among hydrolytic enzymes are: (1) *urease*, which causes the splitting of urea to ammonia and carbon dioxide; (2) *esterases* (*phosphatases*, splitting phosphoric esters; *sulfatases*, splitting sulfate esters; and *lipases*, from castor bean, liver, etc., splitting neutral fats); (3) *carbohydrases* (*amylase*, from saliva and the pancreas, hydrolyzing starch; *invertase*, from yeast, hydrolyzing sucrose); (4) *proteases* (*pepsin*, from the gastric mucosa, causing hydrolysis of certain peptide bonds, such as those between aminodicarboxylic acids and tyrosine; *trypsin*, from the pancreas, attacking those peptide bonds the carbonyl groups of which are furnished by arginine or lysine; *chymotrypsin*, also from the pancreas, attacking those furnished by methionine, phenylalanine, tyrosine, or tryptophane; *papain*, from the papaya, attacking many peptide bonds). A number of enzymes have been obtained crystalline, among them urease (the first one), lipase from liver, pepsin, trypsin, chymotrypsin, and papain.

Hormones may be simple molecules, for example, adrenalin (p. 684) and the steroid hormones; however, many are proteins, such as those of the pancreas, the thyroid gland, the parathyroid glands, and the pituitary gland (hypophysis). Many are conjugated proteins, some are not. Some important protein hormones that have been obtained crystalline are: *thyroglobulin*,

the active principle of the thyroid gland, having thyroxine (p. 589) as the prosthetic group; *insulin*, an active principle from the pancreas, a deficiency of which leads to the symptoms of *diabetes mellitus;* the *growth hormone* of the pituitary gland; and a number of other hormones of this gland.

Antibodies are soluble or insoluble proteins. The soluble type are globulins, mainly. Antibodies have been synthesized in the body so as to have a particular orientation of the peptide chain. This orientation is such that the protein is able to form a complex with some part of the toxin. Also, the antibody has two or more places along the peptide chain where such a reaction can take place. Thus it can combine with two or more toxin units, and since the toxin has two or more reactive positions, it in turn is attacked by two or more protein molecules. Thus an extended framework is formed consisting of toxin and antibody. This, because of its size, is insoluble. In this way the toxin is made inactive.

Viruses are like nucleoproteins, having both protein and nucleic acids in their structures. Viruses are the causative agent of a number of serious diseases. In man these include, among others, the common cold, dengue fever, encephalitis (some types), influenza, measles, mumps, poliomyelitis, smallpox, yellow fever, and virus pneumonia; in animals, cattle plague, foot-and-mouth disease (cattle), Newcastle disease (chickens), distemper (dogs), rabies (dogs), cholera (hogs), and encephalitis (horses); in plants, turnip yellow mosaic, tobacco mosaic, and tomato bushy stunt.

PROBLEMS

1. Show how the following L-peptides may be synthesized from L-amino acids.

a) alanylalanine
b) alanylmethionine
c) alanylproline
d) leucylproline
e) leucylmethionine
f) prolylalanine
g) prolylmethionine
h) prolylproline
i) dialanylproline
j) dialanylmethionine
k) alanylprolylproline
l) alanylprolylalanine
m) prolylalanylalanine
n) diprolylalanine
o) diprolylmethionine
p) leucylprolylmethionine

2. Show how the following DL-peptides may be synthesized, starting with unsubstituted acids:

a) glycylalanine
b) glycylvaline
c) glycylleucine
d) glycylnorvaline
e) glycylnorleucine
f) alanylalanine
g) alanylvaline
h) alanylleucine
i) alanylnorleucine
j) alanylglycylglycine
k) valylglycylglycine
l) diglycylvaline
m) diglycylleucine
n) diglycylnorvaline
o) glycylalanylvaline
p) glycylalanylleucine
q) alanylglycylvaline
r) alanylglycylleucine
s) dialanylleucine
t) dialanylnorleucine

3. For the protein named, calculate from the per cent recovery of histidine, lysine, tryptophane, and tyrosine (Table 100), four minimum molecular weights, neglecting the fact that water is absorbed during the hydrolysis. Calculate also the molecular ratio (in numbers above unity) of the amino acids to each other, taking one of these as unity. On the assumption that the maximum error is ± 2 per cent, calculate a reasonable minimum molecular weight for the protein on the basis of all four values.

a) edestin
b) fibrinogen
c) gliadin
d) insulin
e) lactoglobulin
f) ovalbumin

4. Ditto, but from the arginine, cystine, threonine, and valine content.

a) edestin
b) fibrinogen
c) insulin
d) lactoglobulin

5. Indicate the possible dipeptides, including stereoisomeric forms, derivable from the optically inactive forms of the following:

a) glycine and/or lysine
b) glycine and/or glutamic acid
c) glycine and/or tryptophane
d) histidine and/or proline
e) arginine and/or leucine
f) aspartic acid and/or serine
g) methionine and/or thyroxine
h) glycine and/or cystine
i) glycine and/or hydroxyproline
j) tyrosine and/or cystine
k) glycine and/or threonine
l) alanine and/or threonine

CHAPTER 42

Carbohydrates

The carbohydrates comprise an important group of widely occurring compounds which includes sugars, starches, gums, and cellulose. The compounds of this group are intimately connected with the life processes of plants. The sap contains sugar, which has been elaborated in the leaves out of carbon dioxide and water by the process of photosynthesis. From the sugar the plant synthesizes starches, which are reserve food, and cellulose, which forms the framework of trunks and stems. These substances are of great importance to humans, for the sugars and starches are valuable foods, and cellulose, in the form of cotton, wood, paper, rayon, etc., is an important industrial product.

Chemically the carbohydrates are hydroxy aldehydes or hydroxy ketones or compounds which can be hydrolyzed to them. The name carbohydrate was given because it was early recognized that their formulas correspond to the general one $C_m(H_2O)_n$ (hydrate of carbon); for example, glucose is $C_6H_{12}O_6$, sucrose is $C_{12}H_{22}O_{11}$, and starch is $(C_6H_{10}O_5)_n$. Although it is now known that all carbohydrates do not correspond to this formula (the sugar, rhamnose, is $C_6H_{12}O_5$) and many compounds which are not carbohydrates do (acetic acid is $C_2H_4O_2$ and lactic acid is $C_3H_6O_3$), nevertheless the name has been retained, although the name saccharide has been preferred by some to the name carbohydrate.

Classification. Carbohydrates are classified on the basis of the number of monosaccharide units (or residues) in the molecule of the carbohydrate.

1. *Monosaccharides.* These are simple sugars (glucose, fructose, mannose, etc.). They are soluble in water. They do not undergo hydrolysis to simpler compounds.

2. *Oligosaccharides* (Gr. *oligos*, a few). These have more than one, but very much less than the large number of hexose units characteristic of polysaccharides. The upper limit is not a fixed number, but usually is regarded as less than ten, for this permits inclusion of all of those that are well defined. On hydrolysis they are converted into monosaccharides. The members of this group are subdivided into:

a) *Disaccharides.* A molecule has two monosaccharide units. This is

the most important group of oligosaccharides (sucrose, maltose). Most are readily soluble in water.

b) Trisaccharides. A molecule has three monosaccharide units (raffinose).

3. *Polysaccharides.* These are substances of high molecular weight yielding many molecules of monosaccharide (starch, cellulose, mannan). Polysaccharides, unlike the sugars, are insoluble in water, but some form colloidal solutions (starch, glycogen, inulin).

MONOSACCHARIDES

In these hydroxy aldehydes and hydroxy ketones the carbonyl group is adjacent to one of the hydroxyl groups. They are called respectively aldoses and ketoses. According to the number of carbon atoms they are classified as bioses, trioses, tetroses, pentoses, and hexoses. If a sugar is an aldose and also a pentose, it is called an aldopentose, if a ketose and a hexose, it is called a ketohexose, etc.

		ALDOSES	2-KETOSES
biose	$C_2H_4O_2$	CH_2OHCHO	
triose	$C_3H_6O_3$	$CH_2OHCHOHCHO$	$CH_2OHCOCH_2OH$
tetrose	$C_4H_8O_4$	$CH_2OH(CHOH)_2CHO$	$CH_2OHCHOHCOCH_2OH$
pentose	$C_5H_{10}O_5$	$CH_2OH(CHOH)_3CHO$	$CH_2OH(CHOH)_2COCH_2OH$
hexose	$C_6H_{12}O_6$	$CH_2OH(CHOH)_4CHO$	$CH_2OH(CHOH)_3COCH_2OH$

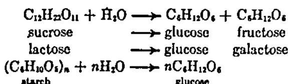
In all of these formulas there is one oxygen atom attached to each carbon atom. There are a number of exceptions, for example, rhamnose, $CH_3(CHOH)_4CHO$. This is called a deoxyhexose. There are other types of ketoses with the carbonyl group on a higher numbered carbon atom. The naturally occurring monosaccharides are pentoses, hexoses, and two heptoses. All these have a normal carbon chain with the exception of one or two minor sugars. Monosaccharides have been synthesized up to and including decose, $C_{10}H_{20}O_{10}$.

With the exception of the simplest aldose and ketose, *viz.*, glyoxylic aldehyde and dihydroxyacetone, all monosaccharides have one or more asymmetric carbon atoms. All those that occur naturally possess optical activity. The hexoses are the most important of the monosaccharides; of these glucose, an aldohexose, is the most important, and fructose, a ketohexose, is the second most important. In Tables 101 and 102 (pp. 615, 616) are listed the important monosaccharides, *viz.*, the pentoses and hexoses. Since the aldopentose molecule has three asymmetric carbon atoms, there are eight stereoisomers, and since the aldohexose molecule has four asymmetric carbon atoms, there are sixteen stereoisomers having the aldehyde structure. Only those of the D family are listed. One of the most important constants of sugars is the specific rotation (p. 299).

D(+)-Glucose, Dextrose, Grape Sugar, $C_6H_{12}O_6$. This is the most widely distributed of the monosaccharides. It occurs in many fruits, especially grapes, and is present in the blood and urine. The blood of normal

persons contains about 0.1 per cent of glucose. In the blood of persons suffering from *diabetes mellitus*, the value may rise as high as 1.2 per cent. Glucose occurs in combination with other substances as glucosides; for example, myosin in mustard, amygdalin in almonds, tannin in bark, anthocyanidins, the coloring matter in many flowers, etc. These substances on hydrolysis yield glucose along with some other product: allyl isothiocyanate from myosin, benzaldehyde and hydrocyanic acid from amygdalin, gallic acid from tannin, and anthocyanins from anthocyanidins.

Glucose is also obtained by the hydrolysis of many di- and polysaccharides, such as sucrose, lactose, starch, and cellulose.



$$C_{12}H_{22}O_{11} + H_2O \longrightarrow C_6H_{12}O_6 + C_6H_{12}O_6$$

sucrose ⟶ glucose fructose

lactose ⟶ glucose galactose

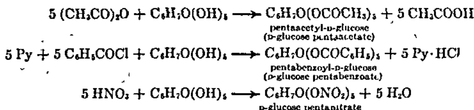
$$\underset{\text{starch}}{(C_6H_{10}O_5)_n} + nH_2O \longrightarrow \underset{\text{glucose}}{nC_6H_{12}O_6}$$

It is manufactured from starch by hydrolysis with dilute hydrochloric acid under pressure at temperatures above 100° and is marketed in the form of sirup, powder, or cakes.

Two forms of glucose are known, called respectively α-D-glucose and β-D-glucose. (See Table 102.) The *alpha*-form of D-glucose is obtained as the hydrate $C_6H_{12}O_6 + H_2O$ when the sugar crystallizes from a cold, saturated aqueous solution. Glucose separates as anhydrous crystals from boiling ethyl alcohol. The *beta*-form is obtained by crystallization from a pyridine solution in the cold or by evaporation of a boiling acetic acid solution of the sugar. When dissolved separately in pure water, each form has its own specific rotation which slowly changes until it reaches the constant value of +52.7° This phenomenon, which is known as **mutarotation**, is shown by many other sugars (Tables 101, 102). The rotation of +52.7° corresponds to the amounts of the isomeric forms of D-glucose that are in equilibrium with each other in solution.

Reactions and Structure of D-Glucose

1. *Ester formation.* Typical compounds are the pentaacetate, pentabenzoate, and pentanitrate.

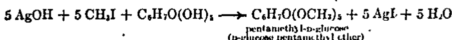


$$5\,(CH_3CO)_2O + C_6H_7O(OH)_5 \longrightarrow \underset{\substack{\text{pentaacetyl-D-glucose}\\ \text{(D-glucose pentaacetate)}}}{C_6H_7O(OCOCH_3)_5} + 5\,CH_3COOH$$

$$5\,Py + 5\,C_6H_5COCl + C_6H_7O(OH)_5 \longrightarrow \underset{\substack{\text{pentabenzoyl-D-glucose}\\ \text{(D-glucose pentabenzoate)}}}{C_6H_7O(OCOC_6H_5)_5} + 5\,Py\cdot HCl$$

$$5\,HNO_3 + C_6H_7O(OH)_5 \longrightarrow \underset{\text{D-glucose pentanitrate}}{C_6H_7O(ONO_2)_5} + 5\,H_2O$$

2. *Ether formation.* Usual alkylating agents (dimethyl sulfate and alkali, for example) may yield products ranging from monoethers to tetraethers. With methyl iodide and silver oxide a pentamethyl ether can be obtained.



$$5\,AgOH + 5\,CH_3I + C_6H_7O(OH)_5 \longrightarrow \underset{\substack{\text{pentamethyl-D-glucose}\\ \text{(D-glucose pentamethyl ether)}}}{C_6H_7O(OCH_3)_5} + 5\,AgI + 5\,H_2O$$

These reactions indicate the presence of five hydroxyl groups in the glucose molecule.

3. *Oxidation.* Glucose is oxidized by ammoniacal silver solution and by hot Fehling's solution. The reduction of silver ion to metallic silver by glucose or other reducing sugar is the usual method of producing silver mirrors on glass. Reduction of Fehling's solution is a characteristic reaction of so-called reducing sugars.

Controlled oxidation of glucose with aqueous bromine leads to the formation of gluconic acid; calcium carbonate is added to react with the hydrobromic acid formed.

$$3\,CaCO_3 + 2\,Br_2 + 2\,(HO)_5C_5H_6{-}CHO \longrightarrow \underset{\text{calcium D-gluconate}}{[(HO)_5C_5H_6{-}CO_2]_2Ca} + 2\,CaBr_2 + 3\,CO_2 + H_2O$$

$$H_2SO_4 + [(HO)_5C_5H_6CO_2]_2Ca \longrightarrow 2\,\underset{\text{D-gluconic acid}}{(HO)_5C_5H_6COOH} + CaSO_4$$

$$(HO)_5C_5H_6COOH \longrightarrow \underset{\text{D-glucono-}\gamma\text{-lactone}}{(HO)_4C_5H_6COO} + H_2O$$

The oxidation can be accomplished with an equimolar amount of bromine. The formation of an acid by this amount indicates the presence of an aldehyde function in the glucose molecule. When attempt is made to obtain the free acid, after calcium has been removed by the proper amount of sulfuric acid, the compound that separates on evaporation is the lactone, owing to its lower solubility, rather than the acid.

A different result is obtained when oxidation with bromine is accomplished in the presence of barium carbonate (p. 629). This is important in connection with the ring structure of glucose.

Oxidation of D-gluconic acid with dilute nitric acid gives the dibasic acid, saccharic acid, usually isolated as a lactone.

$$2\,[O] + \underset{\text{D-gluconic acid}}{HOCH_2{-}C_4H_4(OH)_4{-}COOH} \longrightarrow \underset{\text{D-saccharic acid}}{HOOC{-}C_4H_4(OH)_4{-}COOH} + H_2O$$

A primary alcohol function in gluconic acid, and thus in glucose, is indicated by this reaction.

4. *Reduction.* Sodium amalgam with water reduces D-glucose to D-sorbitol (Table 107, p. 635). Acid is added, to neutralize the base produced.

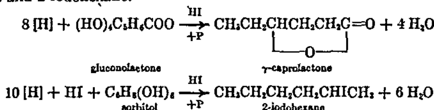
$$2\,Na + 2\,H_2O + (HO)_5C_5H_6{-}CHO \longrightarrow \underset{\text{D-sorbitol}}{C_6H_8(OH)_6} + 2\,NaOH$$

The presence of six hydroxyl groups in the sorbitol molecule is shown by its conversion to the hexaacetyl and similar derivatives.

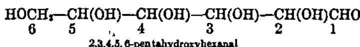
$$6\,(CH_3CO)_2O + C_6H_8(OH)_6 \longrightarrow \underset{\substack{\text{hexaacetyl-D-sorbitol}\\ \text{(D-sorbitol hexaacetate)}}}{C_6H_8(OCOCH_3)_6} + 6\,CH_3COOH$$

Thus an aldehyde function is indicated by oxidation of glucose to an acid and reduction to an alcohol.

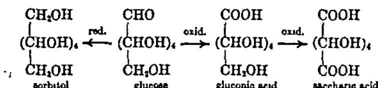
5. *Reduction of hydroxy groups; aldehydo structure of glucose.* When glucono-γ-lactone and sorbitol are separately reduced by heating with hydriodic acid and red phosphorus, reduction products are, respectively, γ-*n*-caprolactone and 2-iodohexane.



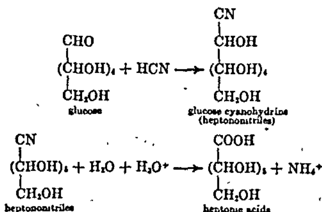
A normal carbon chain is thus indicated for these compounds, and therefore for glucose. Since compounds are unstable when two hydroxyl groups are attached to one carbon atom, a possible structure of glucose, and one proposed early is 2,3,4,5,6-pentahydroxyhexanal.



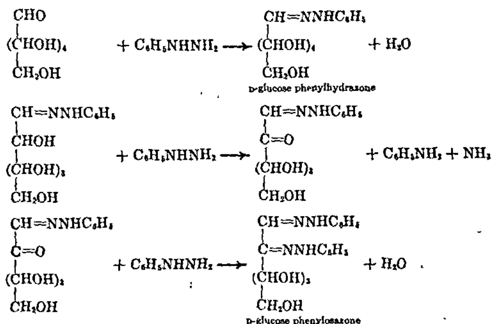
The numbering of the carbon chain starts at the aldehyde end. Although this structure is inadequate because it does not account for the *alpha*- and *beta*-forms of glucose, it will be shown later that the configuration of glucose must first be expressed in terms of the aldehydo (acyclic) structure before the cyclic structure, which accounts for the *alpha*- and *beta-forms*, can be considered. The oxidation and reduction reactions just mentioned can be summarized in terms of acylic structures.



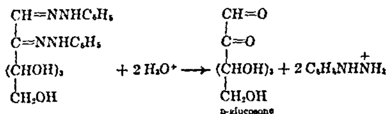
6. *Addition of hydrogen cyanide.* The reaction of this with glucose is a typical step in the synthesis of higher sugars from lower sugars. The resulting cyanohydrins are hydrolyzed to acids.



7. *Reaction with phenylhydrazine; glucosazone; glucosone.* When glucose and excess phenylhydrazine are heated in dilute aqueous solution containing acetic acid, a yellow solid slowly separates out. This is glucosazone. The first reaction product, glucose phenylhydrazone, is very soluble in water. It can only be prepared by working with concentrated solutions. It is oxidized when heated with an excess of phenylhydrazine to an intermediate ketonic compound, and phenylhydrazine is reduced to aniline and ammonia. The ketonic compound reacts with more phenylhydrazine, yielding finally a yellow solid sparingly soluble in water, D-glucose phenylosazone.



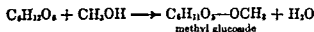
The phenylhydrazine residues can be removed by hydrolysis with concentrated hydrochloric acid.



The reaction of sugars with phenylhydrazine, discovered by Emil Fischer in 1884, has been of great value, because the products formed, being solids sparingly soluble in water, serve as means of distinguishing sugars through melting points and optical rotations. Other reagents are used also; for example, *p*-bromophenylhydrazine, which gives slightly soluble *p*-bromophenylhydrazones with many sugars.

8. *Reaction with alcohols.* Glucose reacts with one molecule of an alcohol in the presence of a strong acid, preferably hydrogen chloride, about 0.5 per

cent. The product is called a glucoside; for example, methanol yields a complex mixture of *alpha*- and *beta*-forms of methyl glucosides.



$$C_6H_{12}O_6 + CH_3OH \longrightarrow \underset{\text{methyl glucoside}}{C_6H_{11}O_5\text{—}OCH_3} + H_2O$$

The methoxy group is attached to carbon atom C-1. The glucosides produced this way have cyclic structures (p. 628) — furanose mainly, at room temperature; pyranose mainly, when heated.

9. *Negative reactions.* Unlike aldehydes in general, glucose does not give a color test with Schiff's reagent, it does not react with sodium bisulfite, and it is not oxidized by the oxygen of the air. The ring structure, described later, accounts for the difference.

TABLE 101 | **Constants of Some Aldopentoses and Pentonic Acids** [a]

	M.P. °C	$[\alpha]^{20}_D$ initial	$[\alpha]^{20}_D$ final
	ALDOPENTOSES ($C_5H_{10}O_5$)		
β-L-Arabinose	160	+190.6	+104.5
α-D-Lyxose	106–107	+5.6	−13.8
β-D-Lyxose	117–118	−72.6	−13.8
D-Ribose	87	−23.1	−23.7 (1°)
L-Ribose	87	+20.3	+20.7
α-D-Xylose	145	+93.6	+18.8
PENTONIC ACIDS ($C_5H_{10}O_6$) AND LACTONES ($C_5H_8O_5$)			
L-Arabonic acid	111–116		−9.8
L-Arabonic γ-lactone	95–98		−71.5
D-Lyxonic acid		+6.6	[illegible]
D-Lyxonic lactone	113–114		[illegible]
D-Ribonic lactone	77		-
L-Ribonic acid	104–105	+17.6	[illegible]
L-Ribonic lactone	79–80		[illegible]
D-Xylonic γ-lactone	98–101		[illegible]

[a] From *Polarimetry, Saccharimetry, and the Sugars*, by F. J. [illegible] [illegible] C–440, National Bureau of Standards, Washington, D. C., [illegible]

next the dibasic acid, D-*manno*-saccharic acid; reduction gives D-mannitol (Table 107); hydrogen cyanide gives D-mannose cyanohydrin, which can be converted to heptonic acids; and methanolic hydrogen chloride gives α- and β-methyl-D-mannoside.

TABLE 102 | **Constants of Some Hexoses and Hexonic Acids**[a]

	M.P. °C	$[\alpha]^{20}_D$ initial	$[\alpha]^{20}_D$ final
	ALDOHEXOSES ($C_6H_{12}O_6$)		
β-D-Allose	128–128.5	−0.2	+14.4
β-L-Allose	128–129	−1.9	−13.9
β-D-Altrose	103–105		+32.6
β-L-Altrose	107–109	−28.8	−32.6
α-D-Galactose	167	+150.7	+80.2
β-D-Galactose		+52.8	+80.2
α-D-Glucose	146	+112.2	+52.7
α-D-Glucose·H_2O	83	+102.0	+47.9
β-D-Glucose	148–150	+18.7	−52.7
α-D-Gulose·$CaCl_2$·H_2O	205	+37.1	−10
α-D-Mannose	133	+29.3	+14.2
β-D-Mannose	132	−17.0	+14.2
α-D-Talose	133–134	+68.0	+20.8
β-D-Talose	120–121	+13.2	+21.0
	KETOHEXOSES ($C_6H_{12}O_6$)		
β-D-Fructose	102–104	−132.2	−92.4
L-Sorbose	159–161	−43.7	−43.4
	HEXONIC ACIDS ($C_6H_{12}O_7$) AND LACTONES ($C_6H_{10}O_6$)		
D-Allonic γ-lactone	97–120		−6.8
L-Allonic γ-lactone	130		+6.3 (25°)
L-Altronic acid	110		−8.1
D-Galactonic acid	148		−13.6
D-Galactonic γ-lactone	133–135 (110–112)		−77.4
D-Gluconic acid	120–131	−6.7	+17.5
D-Gluconic γ-lactone	133–135	+67.5	+17.7
D-Gluconic δ-lactone	150–152	+66.2	+15.8[b]
D-Gulonic γ-lactone	182–185		−57.1
D-Mannonic γ-lactone	151–152		+51.5
D-Mannonic δ-lactone	158–160	+111.8	+30.3
D-Talonic acid·½ H_2O	138		+19.0 (25°)
D-Talonic γ-lactone	132–134		−34.7 (25°)

[a] From *Polarimetry, Saccharimetry, and the Sugars*, by F. J. Bates and Associates, Circular C–440, National Bureau of Standards, Washington, D. C., 1942.
[b] After 25 days; equilibrium not reached.

The main difference between glucose and mannose is in the reaction with phenylhydrazine. Mannose gives colorless mannose phenylhydrazone, which is only very slightly soluble in hot water. However, continued heating with excess phenylhydra-

zine slowly converts this to D-mannose phenylosazone, which is identical with D-glucose phenylosazone.

D(+)-**Galactose.** This is another isomeric aldohexose. It occurs in milk in combination with glucose as the disaccharide, lactose (milk sugar). It occurs also in many gums and resins in the form of high molecular weight compounds, usually in combination with other carbohydrates. *Polymers that yield mainly* galactose on
α- and
h dilute
l, mucic
acid. L(−)-Galactose is found in some gums.

D(−)-Fructose, Levulose, Fruit Sugar, $C_6H_{12}O_6$. This ketohexose is second in importance only to D-glucose among the monosaccharides. It occurs free in the juices of fruits, and in combination with glucose in the most important disaccharide, sucrose. The polysaccharide, inulin, found in the tubers of dahlias and Jerusalem artichokes is derived from fructose and yields fructose on hydrolysis. Fructose is sweeter than glucose or sucrose and because of its greater solubility is not so easily obtained pure.

Fructose resembles glucose chemically in many respects. It reduces silver ion and hot Fehling's solution, and is thus a *reducing sugar*. It forms a pentaacetate and pentamethyl ether, is reduced to the alcohols, mannitol and sorbitol (Table 107), reacts with hydrogen cyanide to form a cyanohydrin, and is converted into a mixture of α- and β-methyl-D-fructosides by methanolic hydrogen chloride. The main differences from glucose are the existence of only one form, *viz.*, the β-form, the reactions with oxidizing agents, and the greater speed of the reaction with phenylhydrazine.

Mild oxidization with mercuric oxide in the presence of barium hydroxide causes scission of the carbon chain by the formation of two acids, glycolic and trihydroxybutyric acids.

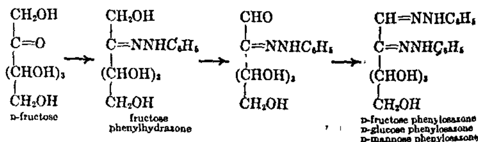
$$\begin{array}{ccccc} CH_2OH & & CH_2OH & & CH_2OH \\ | & & | & & | \\ C{=}O & & COOH & & CHOH \\ | & & & & | \\ CHOH & \longrightarrow & COOH & \longleftarrow & C{=}O \\ | & & | & & | \\ (CHOH)_2 & & (CHOH)_2 & & (CHOH)_2 \\ | & & | & & | \\ CH_2OH & & CH_2OH & & CH_2OH \end{array}$$

This result shows that fructose is a ketohexose and that the carbonyl group is on either carbon atom C-2 or C-3. Its position on C-2 is established by reduction of the heptonic acid resulting from hydrolysis of fructose cyanohydrin.

$$\underset{\text{fructose}}{C_6H_{12}O_6} \xrightarrow{HCN} \underset{\text{fructose cyanohydrin}}{C_6H_{12}O_6{-}CN} \xrightarrow{H_3O^+} C_6H_{12}O_6{-}COOH \xrightarrow[P]{HI} \underset{\text{2-methylhexanoic acid}}{CH_3{-}CH_2{-}CH_2{-}CH_2{-}\underset{\displaystyle COOH}{\underset{|}{CH}}{-}CH_3}$$

The formation of 2-methylhexanoic acid shows that the carbonyl group of fructose is on carbon atom C-2.

An excess of phenylhydrazine converts fructose into an osazone. The reaction proceeds more rapidly than with glucose. The products of the stepwise reactions are shown, but only the osazone separates.



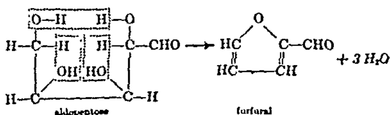
The final product is identical with the osazone obtained from both D-glucose and D-mannose.

Aldopentoses. Three aldopentoses occur naturally, namely, L(+)-arabinose, D(+)-xylose, and D(−)-ribose. Arabinose and xylose are widely distributed and occur as polysaccharides called arabans and xylans, respectively. Polysaccharides yielding pentoses on hydrolysis are known collectively as pentosans. Arabinose is found in gum arabic (hence the name), mesquite gum, cherry gum, and many other plant gums; D-arabinose occurs to a minor extent.

Xylose is obtainable from wood gum (xylan; Gr. *xylon*, wood) on hydrolysis. The best sources are oat hulls, corncobs, cottonseed hulls, and other similar products. Ribose is found in combination with other substances in nucleic acids, present in all living cells. The ribityl radical (from the alcohol) is found in riboflavin (p. 694) and other natural products.

Chemically the aldopentoses resemble glucose. They are reducing sugars, exist in α- and β-forms, and can be acetylated. However, they yield tetraacetates, tetramethyl ethers, etc. The pentoses can be oxidized to monocarboxylic and dicarboxylic acids of five carbon atoms; they undergo the cyanohydrin reaction and yield osazones with phenylhydrazine.

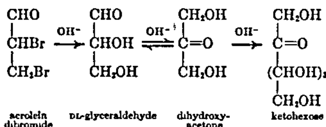
The pentosans, although they are not broken down by the enzymes that hydrolyze starch (and on that account are not readily digested by animals), are hydrolyzed by heating with very dilute mineral acids. If the acid concentration is high, the pentoses formed on hydrolysis may undergo decomposition and yield furfuraldehyde (Furfural, p. 663). This reaction is practically quantitative if the pentosan is heated with concentrated hydrochloric acid.



The furfural distils over. It can be quantitatively determined by color reactions, as for example the ones with aniline or phloroglucinol. A quantitative method for the determination of pentoses and pentosans is based on these reactions. Hexoses do not give furfural under this treatment.

SYNTHESIS OF MONOSACCHARIDES

Formose; Acrose. Formose is the name given to a complex mixture of sugars formed from aqueous formaldehyde under weakly alkaline conditions (p. 281); and acrose is the name given to a less complex mixture resulting from the action of dilute base on acrolein dibromide. In this case the dibromide is converted to DL-glyceraldehyde and dihydroxyacetone by the base (see p. 628) and these two condense to form a ketohexose.



Emil Fischer and his co-workers, by obtaining DL-glucosazone from these mixtures, showed that either one or all of DL-glucose, DL-mannose, or DL-fructose was present. From the osazone they were able to prepare D-glucose, D-mannose, and D-fructose, as well as L-mannose and L-fructose. These results constitute a total synthesis of each of these sugars, since formaldehyde can be obtained from carbon, hydrogen, and oxygen.

Photosynthesis. In the green leaves of plants carbon dioxide and water are converted to glucose and oxygen. This conversion is one of the most important, if not the most important, of known chemical changes. The energy that must be absorbed, since ΔH is +674 kcal., comes from sunlight. The heat of combustion of glucose is 674.0 kcal. per mole.



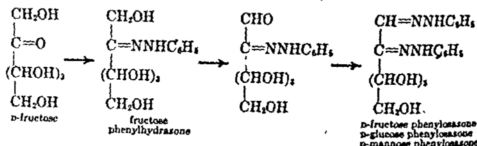
$$6\,CO_2 + 6\,H_2O \longrightarrow C_6H_{12}O_6 + 6\,O_2 \quad \Delta H = +674 \text{ kcal.}$$

The plant converts the glucose into starch, cellulose, or other needed substance. The process of photosynthesis, going on for ages past, has resulted in the conversion of enormous amounts of carbon dioxide into carbohydrates, part of which has undergone chemical change by conversion into other substances such as lignite and coal. Petroleum also, in a more or less roundabout manner, is a product of photosynthesis.

It was proposed years ago by Baeyer that formaldehyde was the first product of photosynthesis and that this then changed to glucose by a process of polymerization, similar to the reaction promoted by alkali, but different in that the plant enzymes direct the reaction asymmetrically, owing to their specific action. This view, widely held at one time, was never substantiated by experiment, since formaldehyde was never isolated as a reaction inter-

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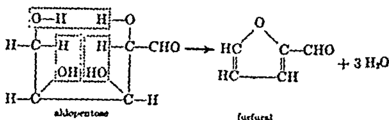
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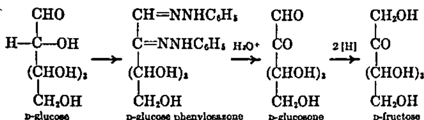
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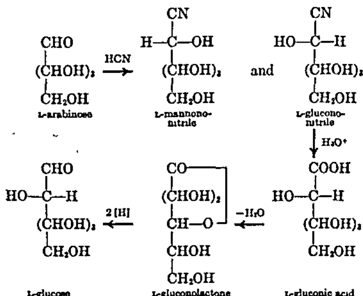
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A 2-Ketose from an Isomeric Aldose. This is accomplished by converting the aldose to the osazone, hydrolysis of this in aqueous acid to the osone, and reduction of the aldehyde function of the osone with zinc and acetic acid.

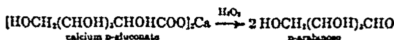


An Aldose from the Next Lower Aldose. This general synthetic method involves reaction of an aldose with hydrogen cyanide to form the aldose *cyanohydrin, hydrolysis of this to the next higher aldonic acid, and reduction of* the aldonic acid to an aldose. Tetroses, however, have not been synthesized this way.



Two cyanohydrins (aldonitriles) are formed in the first reaction, and usually not to the same extent. After they have been hydrolyzed to the acids, separation of the two acids can usually be accomplished by means of salts, often salts with optically active bases, for example, alkaloids. Then each acid can be converted separately to the corresponding aldose.

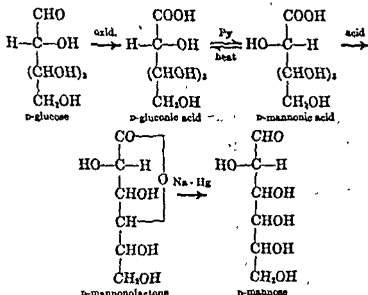
An Aldose from the Next Higher Aldose. This is a process of degradation. There are three methods available, *viz.*, those of Ruff, Weerman, and Wohl. In the method of Ruff, oxidation of the calcium salt of an aldonic acid by hydrogen peroxide in the presence of a ferric salt (ferric acetate) yields the next lower aldose. This method is especially useful for tetroses which are not readily obtainable by the Wohl method.


$$[HOCH_2(CHOH)_3CHOHCOO]_2Ca \xrightarrow{H_2O_2} 2\ HOCH_2(CHOH)_3CHO$$

mediate. The fact that it is a poison to protoplasm would alone make it seem unreasonable.

Recent work by Calvin and others shows that photosynthesis proceeds through a cycle of compounds, mostly two-carbon, three-carbon, and four-carbon compounds. Research along these lines is quite active.

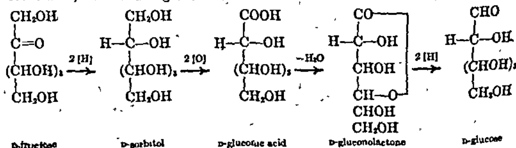
An Aldose from the Epimeric Aldose. Two isomeric aldoses are called epimers when they are identical in all respects except for the configuration about carbon atom C-2. The method is illustrated in the conversion of D-glucose to D-mannose.



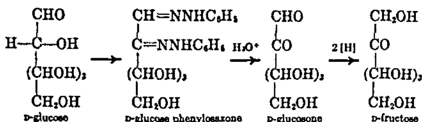
An active α-hydroxy acid undergoes racemization when heated with a base (p. 314). A similar reaction takes place when gluconic acid is heated with the organic base, pyridine (p. 674). Only the configuration about the α-carbon atom is affected. The two acids, gluconic and mannonic, are separated by means of salts, and mannonolactone is reduced in aqueous solution with sodium amalgam. This last step is important as a synthetic method for aldoses, that is, the reduction of the lactone of the corresponding aldonic acid.

It is worth noting that many of the names of sugars are derived from that of the epimeric sugar, to indicate this relationship, for example, talose from galactose, ribose from arabinose, and lyxose from xylose.

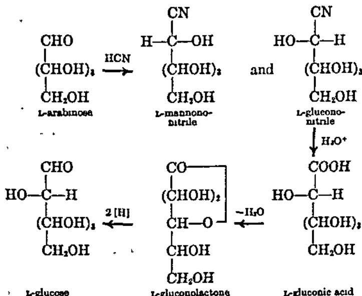
An Aldose from an Isomeric 2-Ketose. This is accomplished by reducing the ketose to the polyhydric alcohol, oxidizing this to the monobasic aldonic acid, and reducing the lactone of this to the aldose.



A 2-Ketose from an Isomeric Aldose. This is accomplished by converting the aldose to the osazone, hydrolysis of this in aqueous acid to the osone, and reduction of the aldehyde function of the osone with zinc and acetic acid.

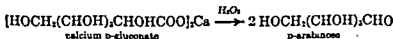


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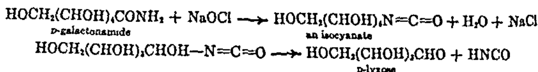


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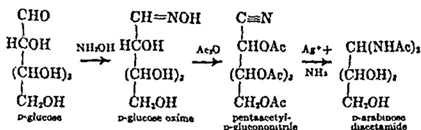
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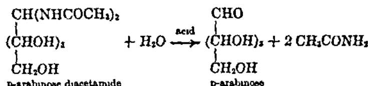
The Weerman method is degradation of an aldonamide by sodium hypochlorite. An intermediate is an isocyanate.



The Wohl degradation is the most important one. An aldose is converted into the oxime and this, with acetic anhydride, gives the nitrile of the aldonic acid, with the hydroxyl groups acetylated. Ammoniacal silver oxide converts this, in alcoholic solution, to a diacetamide derivative of the next lower aldose.



The reaction is essentially the reversal of the cyanohydrin reaction by silver ion through formation of silver cyanide. The acetamide, formed in the ammonolysis of the ester linkages reacts with the aldehyde function of the next lower aldose. This is a *fortunate circumstance because the compound is a solid much less soluble than the aldose. It undergoes hydrolysis to the* aldose.



In one modification of the method ammoniacal silver is replaced by sodium methoxide with chloroform as the solvent.

CONFIGURATIONS OF THE MONOSACCHARIDES

The spatial arrangement of the groups about the asymmetric carbon atoms of the monosaccharides, for its time one of the most difficult of the problems that have arisen in the development of organic chemistry, was established by the German chemist, Emil Fischer, who received the Nobel prize for chemistry in 1902 for this achievement. It is not feasible to trace this line of work as it developed; however, the general method of attack will be described and the results summarized.

Certain facts about each aldose are desirable: (1) its relation to the next lower and next higher aldose; (2) its epimeric sugar; (3) the possession or lack of optical activity in its dibasic acid. The relationship to the next lower (or

next higher) sugar can be obtained either by synthesis or degradation. The latter is more dependable because in synthesis one isomer predominates over the other, owing to the influence of asymmetric synthesis (p. 538), with the result that one may be overlooked. The epimeric relation of two aldoses may be ascertained by synthesis, when both are isolated, or by degradation, in which case both give the same lower aldose, or by the phenylhydrazine reaction, for both yield the same osazone. The lack of rotation in the dibasic acid having the same number of carbon atoms shows that the acid is a *meso*-form (p. 311)

Pentoses and hexoses are the only naturally occurring sugars, except deoxyhexoses and two rare heptoses. The relationships shown in Tables 103, 104, and 105 were established mainly by E. Fischer.

TABLE 103 | **Epimeric Relations of Pentoses and Rotations of Dibasic Acids**

ALDOPENTOSE	DIBASIC ACID			EPIMER	HEXOSE BY HCN
	name	m.p. °C	α^{25}_D		
D(−)-Arabinose	D-*arabo*-Trihydroxyglutaric	128	+27.6	D(−)-Ribose	D-Glucose, D-Mannose
D(−)-Ribose	*ribo*-Trihydroxyglutaric	171 [a]	0 0	D(−)-Arabinose	D-Allose, D-Altrose
D(+)-Xylose	*xylo*-Trihydroxyglutaric	152	0 0	D(−)-Lyxose	D-Gulose, D-Idose
D(−)-Lyxose	D-*arabo*-Trihydroxyglutaric	128	+27.6	D(+)-Xylose	D-Galactose, D-Talose

[a] Lactone.

TABLE 104 | **Epimeric Relations of Aldohexoses and Rotations of Dibasic Acid Lactones**

ALDOHEXOSE	DIBASIC ACID			EPIMER
	name	m p. °C	lactone α^{25}_D	
D-Glucose	D-*gluco*-Saccharic	130 [a]	+22 [a]	D-Mannose
D-Mannose	D-*manno*-Saccharic	180–190 [b]	+204 8 [b]	D-Glucose
D-Galactose	Mucic	217	0	D-Talose
D-Talose	D-*talo*-Mucic	158	+29.4	D-Galactose
D-Gulose	L-*gluco*-Saccharic	?	[c]	D-Idose
D-Idose	D-*ido*-Saccharic	?	−100°?	D-Gulose
D-Allose	*allo*-Mucic	187	0	D-Altrose
D-Altrose	D-*talo*-Mucic	?	+28.5	D-Allose

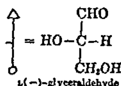
[a] Monolactone. [b] Dilactone. [c] Weakly *levo*.

TABLE 105 | *Epimeric Relations of Some Heptoses and Rotations of Dibasic Acids*

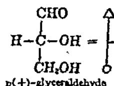
ALDOHEPTOSE	M.P. °C	α^{20}D		DIBASIC ACID		FROM
		initial	final	m.p. °C	α^{20}D	
β-D-α-Glucoheptose	193	−28.7	−20.2	150	0.0	D-Glucose
D-β-Glucoheptose	121	−0.1	−0.1	177	+68.5	D-Glucose
α-D-α-Mannoheptose·H_2O	107	+120.0	+64.7			D-Mannose
β-D-α-Mannoheptose·H_2O	104	+12 3	+64.5			D-Mannose
α-D-β-Mannoheptose·H_2O	83	+45.7	+14.5			D-Mannose

D- and L-Families of Aldoses. The aldoses can be considered to be derived from glyceraldehyde (glyceric aldehyde), $HOCH_2$—CHOH—CHO, a relationship pointed out years ago by E. Fischer and developed more systematically by Rosanoff in 1906. Glyceraldehyde can exist in dextrorotatory and levorotatory forms, owing to the presence of an asymmetric carbon atom in the molecule of glyceraldehyde. Starting with one of the active forms, for example, the *dextro*-form, a reaction with hydrogen cyanide would be expected to yield two tetroses (p. 613), each of these two pentoses, each of these two hexoses, and so on. The operations have been carried as far as decose, but not actually through the tetrose stage.

The two forms of glyceraldehyde are shown below. *Not only are the conventional formulas shown but also abbreviated formulas (sometimes used when it is desirable to save space).* In these the aldehyde function is represented by a triangle, the secondary alcohol function by a short, horizontal line, and the primary alcohol function by a circle.



L(−)-glyceraldehyde



D(+)-glyceraldehyde

The dextrorotatory isomer (often called *d*-glyceraldehyde), when *projected with the H and OH groups towards the observer and the two C—C bonds away from the observer,* is the one with the hydroxyl group on the right, and the levorotatory isomer is the one with this group on the left (p. 300). The nomenclature now preferred for dextrorotatory glyceraldehyde is D(+)-glyceraldehyde, D to indicate that it belongs to the D-family, and (+) to indicate a positive (*dextro*) rotation (p. 302). Conversely, the other isomer is called L(−)-glyceraldehyde.

of sugars. In the D-family the hydroxyl group next to the terminal primary alcohol group lies on the right, and in the L-family it lies on the left. The configuration of the highest numbered asymmetric carbon atom determines

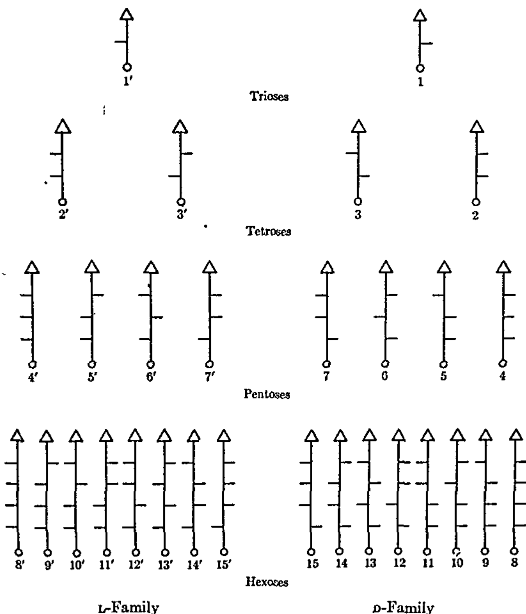


Figure 32 • Aldoses

the family to which the sugar belongs. It is necessary only to present the arguments for establishing the configuration of one of the two families. Fortunately naturally occurring aldoses, with the exception of L(+)-arabinose, and to a minor extent, L(−)-galactose, belong to the D-family.

In Figure 32 are shown aldoses up to and including the hexoses. From Table 103 it is seen that two pentoses, ribose and xylose, yield inactive dibasic acids on oxidation. These are, respectively, *ribo*-trihydroxyglutaric

acid and *xylo*-trihydroxyglutaric acid. Configurations 4 and 6 (Fig. 32) must therefore be reserved for ribose and xylose, since these are the two configurations that are characteristic of the two inactive trihydroxyglutaric acids (p. 316). Each of the other two pentoses, arabinose and lyxose, must have one of the other two possible configurations, 5 and 7.

Arabinose and lyxose can be converted into C_6-dibasic acids by the cyanohydrin reaction, followed by hydrolysis to the monobasic acid and oxidation of this to the dibasic acid. The four possible dibasic acids derived from formulas 5 and 7 must have the configurations shown by 10, 11, 14, and 15 — 10 and 11 from 5, 14 and 15 from 7. Of these four, only 14 can cause internal compensation in a symmetrical molecule such as a dibasic acid. Arabinose yields two active C_6-dibasic acids, and lyxose one active and one inactive C_6-dibasic acid. Thus lyxose must have configuration 7 and arabinose, 5. Ribose is 4, since it is the epimer of arabinose, and xylose is 6, since it is the epimer of lyxose. The degradation of ribose to threose establishes the latter as 3. Erythrose therefore is 2. Erythrose also gives an inactive C_4-dibasic acid on oxidation.

Configurations of the hexoses are narrowed down to two possibilities for each, because of their relationship to the pentoses, as shown in Tables 103 and 104. Thus configurations 8 and 9 must be reserved for allose and altrose, 10 and 11 for glucose and mannose, 12 and 13 for gulose and idose, and 14 and 15 for galactose and talose. Since allose and galactose are the two aldohexoses that yield inactive C_6-dibasic acids, allose must be 8 and galactose 14. Therefore, altrose is 9 and talose is 15.

This leaves the configurations of four aldohexoses to be determined, *viz.*, glucose, mannose, gulose, and idose. The configurations of glucose and mannose were settled by converting them to C_7-dibasic acids. Glucose gave an active and an inactive acid, mannose gave two active acids (Table 105). Glucose therefore is 10 and mannose is 11. Reduction of saccharic acid (the dibasic acid from glucose) gave an aldonic acid, gulonic acid, and reduction of its lactone gave a sugar called gulose, since it came from glucose. This would have a configuration that is the mirror image of 12, *that is, a sugar* of the L-family. Gulose therefore is 12 and idose 13. The complete formulas of the acyclic forms of the aldoses and of fructose are shown in Table 106.

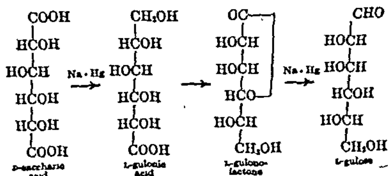
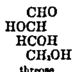
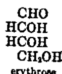


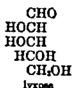
TABLE 106 | Configurations of the D-Aldoses and of D-Fructose

TETROSES

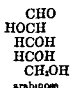

threose

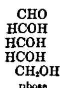

erythrose

PENTOSES

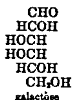

lyxose

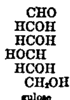

xylose


arabinose

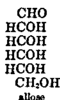

ribose

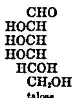
HEXOSES

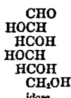

galactose

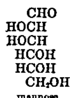

gulose

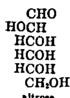

glucose

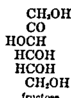

allose


talose

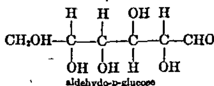

idose

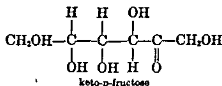

mannose


altrose


fructose

These formulas may be written in the horizontal position, and sometimes this is done in order to conserve space.


aldehydo-D-glucose


keto-D-fructose

Configuration of Fructose. It has been noted already that the phenylosazones of D-glucose, D-mannose, and D-fructose are identical (p. 618). This fact establishes the configuration of fructose, since the configurations about C-3, C-4, and C-5 must be alike for all three sugars.

Effect of Alkali on Sugars. In dilute aqueous alkali a reducing sugar undergoes *profound changes. One of the first effects is isomerization, for example, D-glucose is*

acid and *xylo*-trihydroxyglutaric acid. Configurations 4 and 6 (Fig. 32) must therefore be reserved for ribose and xylose, since these are the two configurations that are characteristic of the two inactive trihydroxyglutaric acids (p. 316). Each of the other two pentoses, arabinose and lyxose, must have one of the other two possible configurations, 5 and 7.

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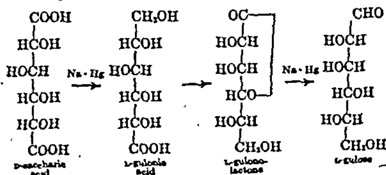
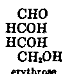


TABLE 106 | **Configurations of the D-Aldoses and of D-Fructose**

TETROSES

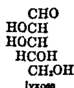


threose

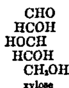


erythrose

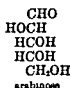
PENTOSES



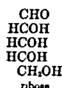
lyxose



xylose

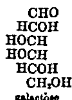


arabinose

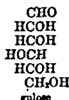


ribose

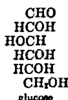
HEXOSES.



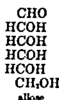
galactose



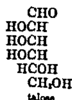
gulose



glucose



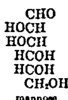
allose



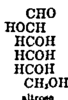
talose



idose



mannose

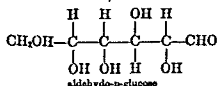


altrose

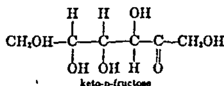


fructose

These formulas may be written in the horizontal position, and sometimes this is done in order to conserve space.



aldehydo-D-glucose



keto-D-fructose

Configuration of Fructose. It has been noted already that the phenylosazones of D-glucose, D-mannose, and D-fructose are identical (p. 618). This fact establishes the configuration of fructose, since the configurations about C-3, C-4, and C-5 must be alike for all three sugars.

Effect of Alkali on Sugars. In dilute aqueous alkali a reducing sugar undergoes profound changes. One of the first effects is isomerization, for example, D-glucose is

in equilibrium with D-mannose and D-fructose. This change is usually accounted for in terms of acyclic structures and is believed to involve *enolization.* The first effect of the base is believed to be the removal of a proton *alpha* to a carbonyl group, thus producing a negative ion (Fig. 33). This is also, by resonance, a *cis*-enolate ion. Because of the presence of the hydroxyl group on the adjacent carbon atom, C-2, the negative charge can move to the oxygen atom there, by a proton shift, and

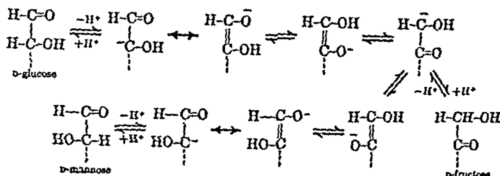
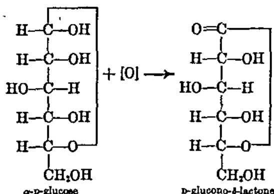


Figure 33 · Equilibrium between Glucose, Mannose, and Fructose under Alkaline Conditions

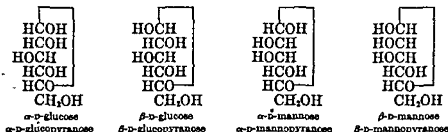
thus lead to the formation of an isomeric anion. This in turn yields either D-fructose by accepting a proton, or D-mannose, by conversion to a *trans*-enolate ion which accepts a proton. The enolization process can move down the carbon chain from the ketose, thus leading to the production of other ketose sugars. Other, more complicated reactions take place, with branching of the carbon chain in some cases, and formation of hydroxy acids, called saccharinic acids. After glucose has stood for some days in 1 *N* potassium hydroxide about 50 per cent has been converted to DL-lactic acid and the rest to a complex mixture of saccharinic acids, $(CH_2O)_n$, where n is 4, 5, and 6.

Isomeric Forms of Sugars and Glycosides; Nomenclature. Most of the monosaccharides and many of the disaccharides exist in *alpha-* and *beta-* forms (Tables 101, 102). Moreover, numerous derivatives also exist in two isomeric forms, for example, the glycosides, the pentamethyl ethers, the pentaacetates, and numerous similar compounds. The existence of isomeric forms necessitates a cyclic structure, a hemiacetal structure arising from the reaction of the aldehyde function with an alcohol function. As a result of this, carbon atom C-1 becomes asymmetric and thus gives rise to two isomers. The union of carbon atom C-1 usually is with carbon atom C-5. This has been established as the result of extensive researches, mainly by the English group of chemists, Haworth, Hirst, and others. The methods have involved methylation of the sugars and determination of the positions occupied by the methyl groups. Usually it was found that the position on carbon atom C-5 was not methylated. The most direct evidence comes from the oxidation of α-D-glucose with aqueous bromine in the presence of barium carbonate and under carefully controlled conditions (short time, vigorous agitation, and saturation with carbon dioxide). The reaction product is D-glucono-δ-lactone (Isbell). This result indicates that oxidation involves changing the CHOH



α-D-glucose D-glucono-δ-lactone

function directly to the C=O function without opening of the ring. In the D-family of aldoses the hydroxyl group attached to C-1 is on the right for the α-sugars and on the left for the β-sugars, as the formulas of the isomeric forms of glucose and mannose show.



α-D-glucose α-D-glucopyranose β-D-glucose β-D-glucopyranose α-D-mannose α-D-mannopyranose β-D-mannose β-D-mannopyranose

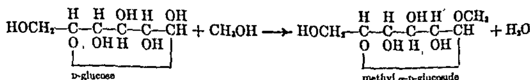
The cyclic structure accounts not only for the existence of the α- and β-sugars and α- and β-glycosides but also for the lowered reactivity of sugars as compared to aldehydes in general (p. 615). The α- and β-forms of the sugars are hemiacetals (p. 266).

The complete names of α-D-glucose and β-D-glucose are, respectively, α-D-glucopyranose and β-D-glucopyranose, to indicate a six-membered ring composed of the same elements as the pyran ring (Chap. 44). This method of nomenclature is desirable in order to distinguish between different ring systems; for example, there are derivatives of a less stable form of glucose formerly called γ-glucose. This has a five-membered ring, the same size as the ring of γ-lactones. This ring is called a furanose ring since it has the same elements as the ring of furan (p. 662).

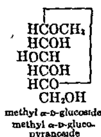
The reactions of glucose have been described in terms of aldehydo-D-glucose, and yet the known forms of glucose have cyclic structures. It often is assumed that there is an equilibrium in solution between aldehydo-D-glucose, α-D-glucose, and β-D-glucose and that the aldehydo isomer is the reactive form. This does not seem to be the case in the oxidation reaction, as shown by the formation of glucono-δ-lactone, and there is evidence that phenylhydrazones may have a cyclic structure. However, in the interest of simplicity the reader may assume that there is enough aldehydo-D-glucose present to account for the reactions. The failure of glucose to react with sodium bisulfite may be due to the low concentration of the acyclic form.

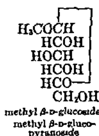
Mutarotation (p. 631) is due to a slow change of an α-sugar to the β-sugar, or *vice versa*, until an equilibrium is reached. This reaction is easily accounted for on the basis of an equilibrium between the aldehydo sugar and the two cyclic forms, but this is difficult to prove.

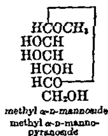
Glycoside is a general name to include glucosides, mannosides, fructosides, etc. Glycosides are obtained from monosaccharides by reaction with an alcohol in the presence of an anhydrous acid, preferably hydrogen chloride (usually 0.5%; see p. 614). The reaction takes place at carbon atom C-1. The products are cyclic mixed acetals. Those from glucose are called glucosides,

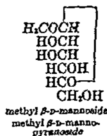


those from mannose, mannosides, etc. *Usually from a given sugar under the acidic conditions prevailing, isomeric glycosides are formed.* Glucose is converted first into the less stable derivatives having a furanose structure and these slowly into the more stable pyranose derivatives. Nomenclature is similar to that of the corresponding sugar. Although usually a name such as methyl α-D-glucoside is sufficient, the complete name should include also the kind of ring, for example, methyl α-D-glucopyranoside.



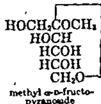


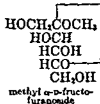




There are α- and β-forms of fructosides and fructose esters but only one isomeric fructose, the β-pyranoside. The stable derivatives in general have pyranose rings, but methyl α-fructofuranoside is known. However, in combination in disaccharides and polysaccharides, fructose occurs as a β-furanoside.







The methyl fructosides undergo hydrolysis thousands of times more rapidly *than the methyl glucosides.* Of the three methyl fructosides, the one having the furanose structure is the most reactive.

Glycosides are quite stable in neutral aqueous solution and undergo hydrolysis in dilute aqueous acid. In nonaqueous solvents such as methanol, hydrogen chloride causes α- and β-glycosides to isomerize to an equilibrium mixture. Glycosides do not reduce Fehling's solution or ammoniacal silver ion.

The α- and β-forms of glucosides differ towards hydrolytic ferments. An enzyme that brings about the hydrolysis of α-glucosides is called an α-glucosidase, and one that acts similarly on a β-glucoside is called a β-glucosidase. Maltase, from malt, causes the hydrolysis of methyl α-D-glucoside and other α-glucosides but not that of methyl β-D-glucoside or other β-glucosides. Emulsin, from bitter almonds (p. 538), promotes the hydrolysis of methyl β-D-glucoside and other β-glucosides but not that of α-glucoside. These two ferments are mixtures of enzymes and the results are not this simple. However, purified α-glucosidases and β-glucosidases are specific in their action.

There are regular differences in the optical rotations of α- and β-isomers of aldoses, their glycosides, and other derivatives. The development of the so-called isorotation rules is due to C. S. Hudson. He has used these rules as an aid in determining the configuration of many sugar derivatives. They are useful in determining the configuration of a glucoside

Derivatives of carbohydrates are named differently from those of other compounds. As an example, the preferred names for glucose pentaacetate and glucose pentamethyl ether are, respectively, pentaacetylglucose and pentamethylglucose. Ordinarily, a derivative of a compound means that the substituent radical takes the place of a hydrogen atom attached to a carbon atom, but in carbohydrate nomenclature it indicates that the radical replaces a hydrogen atom of a hydroxyl group. It has been proposed recently that the position of such a radical be indicated unequivocably by the insertion of the letter, O, in the name. When an alkyl (or aryl) radical is attached through oxygen to C-1, the compound is a glycoside and should be named as such. Thus, instead of the names used earlier, for example, glucose pentamethyl ether and pentamethylglucose, the glycoside name is preferred, *viz.*, methyl 2,3,4,6-tetramethylglucoside. However, this name is still not complete because it does not give the configuration at C-1 nor the ring structure. These are indicated by the name, methyl 2,3,4,6-tetramethyl-α-D-glucopyranoside. If the new proposals are followed, this would be methyl 2,3,4,6-O-tetramethyl-α-D-glucopyranoside.

Glycosides may be converted into acyl derivatives. As an example, methyl α-D-glucopyranoside yields methyl 2,3,4,6-tetraacetyl-α-D-glucopyranoside with acetic anhydride in the presence of a suitable catalyst. This should be a basic catalyst, such as sodium acetate or pyridine, but not an acidic one, such as sulfuric acid, because it may promote mutarotation.

Mutarotation. Each sugar has its own characteristic rotation when dissolved in water. The rotation changes slowly in the direction of the isomeric α- or β-sugar, until finally it reaches a constant value, the one characteristic of the equilibrium mixture containing both sugars. The change is accelerated by the presence of hydrogen ion, hydroxide ion, or anions of weak a

for example, acetate ion. Since a strong base may bring about unwanted changes (p. 628), ammonia is often used for the purpose of hastening the change.

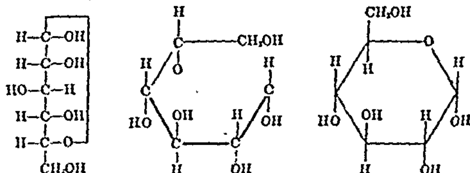
In the D-family the *alpha*-isomer always has the higher positive rotation or, corollarially, the lower negative rotation. If a D-sugar is observed to mutarotate downwards, that is, if the rotation of an aqueous solution becomes less positive or more negative, it has the α-configuration. Conversely, if it mutarotates upwards, it has the β-configuration.

Derivatives of sugars at carbon C-1, as, for example, glycosides or acyl derivatives, do not undergo mutarotation as readily as the sugars. Catalysts that promote this change are strong acids, for example, hydrogen chloride or hydrogen sulfate. Anhydrous zinc chloride in acetic anhydride causes mutarotation of acetates at 100° but very little at 0°. Anhydrous sodium acetate has little effect on acetates, even at 135°.

Acyl Derivatives. An α- or β-sugar can be converted into the corresponding α- or β-acetate under conditions that do not favor mutarotation of the product. With excess acetic anhydride and with pyridine or anhydrous zinc chloride as the catalyst and at temperatures near 0°, α-D-glucopyranose yields pentaacetyl-α-D-glucopyranose, and β-D-glucopyranose yields pentaacetyl-β-D-glucopyranose.

With sulfuric acid as the catalyst both sugars yield the α-pentaacetate because at equilibrium the mixture is 90 per cent α- and 10 per cent β-pentaacetate. With zinc chloride as the catalyst and at 100°, the result is similar. With sodium acetate as the catalyst and at 135°, the product is mainly the β-pentaacetate because the equilibrium mixture of the sugars is 36 per cent α- and 64 per cent β-D-glucose and the β-isomer is the more reactive.

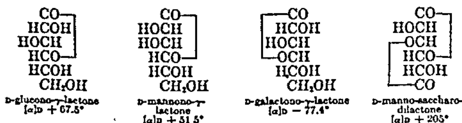
Three-Dimensional Formulas. It often is desirable to show the formulas of sugars in three dimensions. In the case of α-D-glucose, this is done by first discarding the long bond between oxygen and C-1, rotating the vertical formula through 90° and bending the carbon chain backward, thus reversing the standard procedure of projection (p. 300). The heavy lines joining carbon atoms indicate that this part of the chain is closest to the observer. The heavy vertical lines indicate that the attached groups are above the carbon atoms, and the lighter lines, that they are below. Next, the groups about C-5 are rotated, so as to bring the oxygen atom in alignment for completing



the ring. The carbon atoms of the ring are omitted in the final, cyclic struc ture. Similar ring structures can be constructed for other aldohexoses. Al of the pyranose sugars of the D-family are like glucose in having the termina CH_2OH group above the plane of the ring when the oxygen atom is back.

Aldonic Acids. In general, these can be obtained from the aldoses by bromin oxidation in the presence of calcium carbonate or preferably by electrolytic oxidatio in a solution containing some bromide ion, since then there is less metallic salt in solu tion. In general, metallic salts hinder crystallization of sugars or related compounds There is equilibrium in aqueous solution between the acid and its lactones, and sinc a lactone usually is less soluble than the acid, it crystallizes out first. The γ-lacton *is usually obtained this way, since other lactones, being less stable (p. 298), are les* abundant.

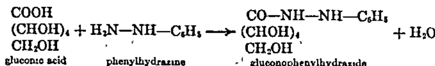
A lactone has a higher rotation than the acid or salts of the acid; for example, th γ-lactone of D-gluconic acid has for $[\alpha]_D$ a value of +68.0° and the magnesium salt ha a value of +10.5°. A compound having two lactone rings, *viz.*, D-mannosaccharodilac tone, has a specific rotation of +205°, an unusually high value.



D-glucono-γ-lactone $[\alpha]_D$ + 67.5° D-mannono-γ-lactone $[\alpha]_D$ + 51.5° D-galactono-γ-lactone $[\alpha]_D$ − 77.4° D-manno-saccharo-dilactone $[\alpha]_D$ + 205°

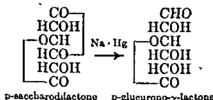
When the oxygen ring of a lactone lies to the right, the lactone is more dextrorotatory than the corresponding acid, and when the ring lies to the left, the lactone is more levorotatory. This holds for δ-lactones, as well as for γ-lactones. In general, the lactone has a positive rotation when the ring lies on the right, and *vice versa* (Tables 101, 102). The lactone of D-allonic acid is one of the few exceptions (α^{20}_D − 6.8°).

The sign of rotation of aldonic amides and aldonic phenylhydrazides is related to the configuration about carbon atom C-2. If the hydroxyl group lies on the right, the rotation is positive, and if on the left, it is negative. A phenylhydrazide is prepared by heating a concentrated aqueous solution of the aldonic acid and phenylhydrazine.



gluconic acid phenylhydrazine gluconophenylhydrazide

Uronic Acids. These are related to the aldoses in having a carboxyl group in place of the terminal CH_2OH group. Glucuronic acid is prepared by the reduction of the dilactone of saccharic acid.



D-saccharodilactone D-glucurono-γ-lactone

Polyhydric Alcohols. These, sometimes called polyols, can be obtained by reduction of the corresponding aldoses; also some are obtained from ketoses, but then a mixture results. Sodium amalgam is the classical reducing agent; hydrogenation usually gives purer products. Some polyols occur in plants; for example, among the pentitols are D-arabitol (rare) and ribitol (uncombined, rare, and combined as a component of riboflavin, Vitamin B_2). Among the hexitols are sorbitol (especially abundant in berries of the mountain ash and very widely distributed), D-mannitol (best from manna of the manna ash and widely distributed), L-iditol (rare), and galactitol (in red seaweed and widespread). Two heptitols also occur naturally.

DISACCHARIDES

The three most important disaccharides are sucrose, maltose, and lactose. Another disaccharide, cellobiose, is important because of its relationship to cellulose.

Sucrose, Cane Sugar, $C_{12}H_{22}O_{11}$. *This is the ordinary sugar of commerce, and* is the best known of the sugars. It occurs in the sap of many plants, especially the sugar cane, sugar beet, sorghum cane, and sugar maple, all of which are utilized for the preparation of the sugar or of a sweet sirup. The two principal commercial sources are the sugar cane and sugar beet. Sucrose is used as a sweetening agent and in the manufacture of confections. It is a food since it will suffer complete oxidation in the body. It is sweeter than glucose and the other sugars with the exception of fructose.

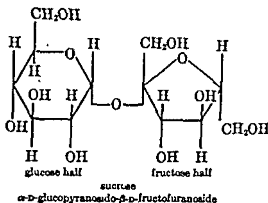
TABLE 107 | Some Polyhydric Alcohols

NAME	M.P. °C	α_D	CONFIGURATION OF
D-Erythritol	201	0.0	erythrose (D or L)
D-Threitol	88	+4.3	D-threose
D-Arabitol	102	+7.82 [a]	D-arabinose
Ribitol	102	0.0	ribose (D or L)
Xylitol	93–94	0.0	xylose (D or L)
Galactitol	188–189	0.0	galactose (D or L)
D-Iditol	73.5	+3.5	D-idose
D-Mannitol	166 (168)	−0.21 (+28.3 [a])	D-mannose
D-Sorbitol	97.5 (135–137)	−1.98 (+6.5 [a])	D-glucose
D-Talitol	86	+3.05	D-talose

[a] Borax.

When heated, sucrose melts to a liquid which on cooling sets to a hard, transparent mass called barley sugar. At temperatures slightly above the melting point, water is lost and the sugar turns dark. The product at this stage is called caramel. Finally, at still higher temperatures, decomposition sets in, all of the hydrogen and oxygen are expelled as water and as other compounds, and there is left behind a residue of pure carbon. Sucrose combines with acids and with acid anhydrides to form esters; with acetic anhydride an octaacetate is formed. This indicates the presence of eight hydroxyl groups in the sucrose molecule. Since no higher acetate can be obtained, the other three oxygen atoms must be constituents of radicals other than hydroxyl groups.

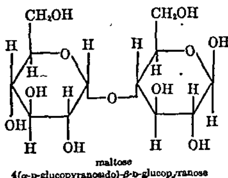
Sucrose is both an α-glucoside and a β-fructoside. The oxide ring in the glucose half



sucrose
α-D-glucopyranosido-β-D-fructofuranoside

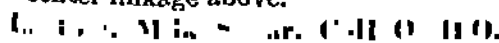
is the ring of ordinary glucose, that is, a pyranose ring, but the ring in the fructose half is not the stable ring characteristic of normal fructose, but a more reactive furanose ring, which changes over during hydrolysis to the more stable pyranose ring.

Maltose, Malt Sugar, $C_{12}H_{22}O_{11}\cdot H_2O$. This is obtained when starch is hydrolyzed by the enzyme diastase which is present in sprouted grains (p. 640). Maltose is hydrolyzed by maltase, an enzyme present in yeast, to D-glucose; the hydrolysis is also brought about by heating the sugar with dilute acids. Maltose reduces Fehling's solution and forms with phenylhydrazine a phenylhydrazone and an osazone. It also exists in α- and β-forms. Maltose therefore has the equivalent of a free aldehyde group. Since it forms an osazone, there must be an uncombined hydroxyl group adjoining the aldehyde group. Maltose can be converted into an octaacetate. Since it is hydrolyzed by maltase and not by emulsin, it has the α-glucosidal structure. The linkage between the two glucose molecules connects the terminal glucosidal carbon of one molecule to the fourth carbon of the other. Maltose is thus a glucosidoglucose.



maltose
4(α-D-glucopyranosido)-β-D-glucopyranose

It is believed that the starch molecule is built up largely of maltose molecules and that the above structure represents the simple unit of which the starch molecule is composed. Other maltose molecules are attached at each end by a union similar to the center linkage above.



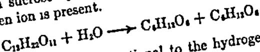
Sucrose is not a reducing sugar, for it has no immediate action upon ammoniacal silver ion nor upon Fehling's solution. This indicates that there is neither an aldehyde nor a ketone function in the molecule. The inability of sucrose to react with phenylhydrazine and the nonexistence of glucosidelike derivatives likewise point to the absence of a free oxo group.

TABLE 108 | Physical Constants of Some Disaccharides

NAME	$[\alpha]_D$, ANHYDROUS			M.P. °C	SOLY. H_2O G./100 G.	SOURCE	HYDROLYZED	
	α	β	equil.				by	to
Sucrose			+66.5 [a]	189	198	sugar cane, etc.	invertase	glucose, fructose
Maltose	+168	+118	+136	125–130(β)	108	starch	maltase	glucose
Lactose	+90	+35	+55	203(α)	17	milk	lactase	glucose, galactose
Cellobiose	+72 [b]	+16	+35	225(β)	12	cellulose	emulsin	glucose
Melibiose	+179 [b]	+124	+143	85–95(β)		raffinose		glucose, galactose
Gentiobiose			−40	125–130(α)	8	amygdalin	emulsin	glucose

[a] Only one form [b] Calculated values.

In aqueous solution sucrose hydrolyzes to a mixture of D(+)-glucose and D(−)-fructose when hydrogen ion is present.



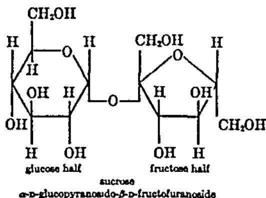
$$C_{12}H_{22}O_{11} + H_2O \longrightarrow C_6H_{12}O_6 + C_6H_{12}O_6$$

The rate of hydrolysis is directly proportional to the hydrogen ion activity at low concentrations, and the reaction has been used for the purpose of determining the activity of hydrogen ion. In fact this reaction was one of the first methods applied to determining acid strengths. The reaction can be followed easily by the polariscope, since the original sucrose solution is dextrorotatory and the resulting solution is levorotatory (D-glucose, +52.7°; D-fructose, −92.4°). Because of th[illegible] ...on in sign the hydrolysis is often called inversion, and the mixture of gl[illegible] ...se is called **invert sugar.** Inversion is also brought about at norma[illegible] ... the enzyme, invertase, which is present in yeast.

Sucrose is a very weak acid, $K_a = 2.4 \times 10^{-12}$, and with [illegible] ...led sucrates. The calcium and strontium salts, because of their l[illegible] ...sed in the sugar industry for separating sucrose from molasses. [illegible] ...e molasses is diluted to about 7 per cent sugar, the solution is [illegible] ...n pulverized lime is added during violent agitation. The tri[illegible] cipitates is added to another batch of sugar cane juice.

Structure of Sucrose. The oxo group in each hexose [illegible] binding them together, since there is no free aldehyde or [illegible] The existence of an octaacetate points to the presence of e[illegible] positions of these hydroxyl groups have been determined b[illegible] of the glucose and fructose derivatives resulting from the h[illegible] tives such as methylsucrose, sucrose acetate, etc. Sucro[illegible]

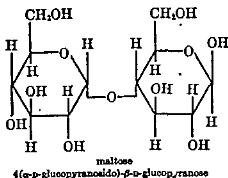
Sucrose is both an α-glucoside and a β-fructoside. The oxide ring in the glucose half



sucrose
α-D-glucopyranosido-β-D-fructofuranoside

is the ring of ordinary glucose, that is, a pyranose ring, but the ring in the fructose half is not the stable ring characteristic of normal fructose, but a more reactive furanose ring, which changes over during hydrolysis to the more stable pyranose ring.

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maltose
4(α-D-glucopyranosido)-β-D-glucopyranose

It is believed that the starch molecule is built up largely of maltose molecules and that the above structure represents the simple unit of which the starch molecule is composed. Other maltose molecules are attached at each end by a union similar to the center linkage above.

Lactose, Milk Sugar, $C_{12}H_{22}O_{11}\cdot H_2O$. This is present in milk. It exists in *alpha*- and *beta*-forms, reduces Fehling's solution, and can be converted into a phenylhydrazone and an osazone. These facts indicate that lactose has the equivalent of a free aldehyde group. The sugar is hydrolyzed by dilute acids to glucose and galactose, whereas the osazone of lactose is split by heating with dilute acids into galactose and

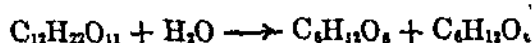
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TABLE 108 | Physical Constants of Some Disaccharid

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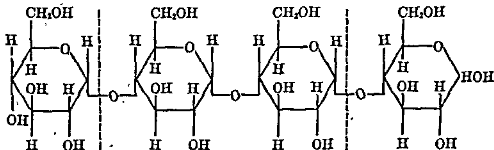
plant of the next generation may have a supply of food until able to shift for itself, and cellulose is a component of the framework of the plant. Or glucose may be converted to some other sugar and this may form the building unit, *e.g.*, mannose in mannan or xylose in xylan.

An approximate formula for a polysaccharide is $(C_6H_{10}O_5)_n$, where n is fairly large. Many different values have been reported, the largest of which vary from 300 to 400 for amylose starch, 1000 to 3500 for cellulose, and 1500 to 20,000 for glycogen. Amylopectin is above 1300. These figures represent the so-called "degree of polymerization," usually abbreviated to D.P.

Starch. This is found in various parts of plants but mainly in seeds or tubers. It is present as small granules which often differ in appearance when viewed under the microscope. The type of starch and the plant from which it comes are often determined by microscopic examination.

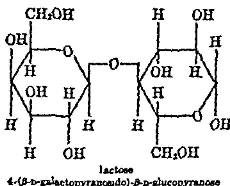
The main use of starch, in the form of grains, is for food. The preparation of starch from grains, such as corn, wheat, rice, etc., and from potatoes is largely mechanical. Thorough grinding breaks down the cellular structure, the starch settles to the bottom, the water is decanted off, and the residue is filtered and dried. Starch is used as a food, as a sizing for cotton cloth, for laundry work, and for the preparation of glucose. Dextrins are used as adhesives and for the sizing of paper and textiles.

Starch is insoluble in cold water, but when heated with water the granules burst and the starch partly diffuses into the liquid, forming a colloidal solution. There are two fractions, *viz.*, **amylose**, the part extractable by hot water, and **amylopectin**, the insoluble portion. Amylose is believed to be simple straight chain starch, built up of maltose units. Amylopectin is believed to have, in addition to the characteristic amylose structure, frequent branching. Molecular weights reported for starch from corn are: amylose, 54,000 to 72,000, and amylopectin, much larger. Values reported for potato amylose and amylopectin are 185,000 and 1,000,000, respectively. On the average there are three hydroxyl groups per glucose unit in starch. These can react to form esters and ethers. Hydrolysis of a completely methylated starch yields 2,3,6-trimethylglucose mainly, with about 4 per cent of 2,3,4,6-tetramethylglucose. The presence of the latter indicates the percentage of glucose units present as "end groups," that is, attached to the rest of the starch molecule only at C-1. The structure of amylose is believed to be a succession of α-maltose residues, where the part between the dotted lines is repeated a large number of times.



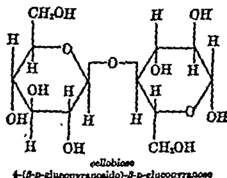
Starch in colloidal solution does not reduce hot Fehling's solution, does not react with phenylhydrazine, and is not fermented by zymase (p. 642). It is hydrolyzed by enzymes called amylases and by heating with acids. Hydrolysis proceeds through a succession of progressively less complex substances called **dextrins** to the final sugar, glucose, some of which is also being formed throughout the process. Maltose is an

glucosazone. This shows that the glucose part of the molecule is able to unite with phenylhydrazine, whereas the galactose part is not. This indicates that the free aldehyde group is in the glucose half. Other evidence indicates that lactose is a β-galactoside, not an α-galactoside. The union is with the fourth carbon atom of the glucose half. Lactose is thus a galactosidoglucose.



lactose
4-(β-D-galactopyranosido)-β-D-glucopyranose

Cellobiose, $C_{12}H_{22}O_{11}$. This is obtained by the hydrolysis of cellobiose octaacetate. The latter compound is formed when cellulose stands for several days with acetic anhydride in the presence of concentrated sulfuric acid. This treatment causes a gradual breakdown of the cellulose molecule and simultaneous acetylation of the fragments. Cellobiose is of interest because it is believed to be the unit from which the cellulose molecule is built. Cellobiose is cleaved by emulsin and is therefore a β-glucoside. The union is with the fourth carbon atom. As isolated, cellobiose is a β-sugar. It is a glucosidoglucose. Cellobiose differs from maltose in being a β-glucoside, whereas maltose is the isomeric α-glucoside.



cellobiose
4-(β-D-glucopyranosido)-β-D-glucopyranose

Trisaccharides. Of the many sugars of this class the most important member is raffinose, which is found along with sucrose in the sugar beet. When hydrolyzed, it yields glucose, fructose, and galactose.

POLYSACCHARIDES

Polysaccharides are substances of high molecular weight formed by the condensation of many molecules of monosaccharides by loss of water. They are found widely distributed in plants in enormous quantities in the form of starch, cellulose, gums, and other materials. The glucose of the plant sap is converted into polysaccharides according to the needs of the plant. Starch is stored in the seeds in order that the young

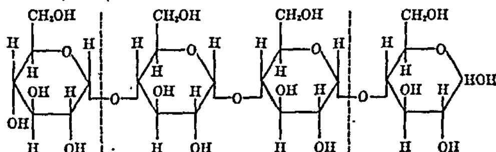
plant of the next generation may have a supply of food until able to shift for itself, and cellulose is a component of the framework of the plant. Or glucose may be converted to some other sugar and this may form the building unit, *e.g.*, mannose in mannan or xylose in xylan.

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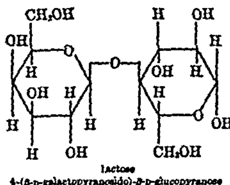
The main use of starch, in the form of grains, is for food. The preparation of starch from grains, such as corn, wheat, rice, etc., and from potatoes is largely mechanical. Thorough grinding breaks down the cellular structure, the starch settles to the bottom, the water is decanted off, and the residue is filtered and dried. Starch is used as a food, as a sizing for cotton cloth, for laundry work, and for the preparation of glucose. Dextrins are used as adhesives and for the sizing of paper and textiles.

Starch is insoluble in cold water, but when heated with water the granules burst and the starch partly diffuses into the liquid, forming a colloidal solution. There are two fractions, *viz.*, **amylose**, the part extractable by hot water, and **amylopectin**, the insoluble portion. Amylose is believed to be simple straight chain starch, built up of maltose units. Amylopectin is believed to have, in addition to the characteristic amylose structure, frequent branching. Molecular weights reported for starch from corn are: amylose, 54,000 to 72,000, and amylopectin, much larger. Values reported for potato amylose and amylopectin are 185,000 and 1,000,000, respectively. On the average there are three hydroxyl groups per glucose unit in starch. These can react to form esters and ethers. Hydrolysis of a completely methylated starch yields 2,3,6-trimethylglucose mainly, with about 4 per cent of 2,3,4,6-tetramethylglucose. The presence of the latter indicates the percentage of glucose units present as "end groups," that is, attached to the rest of the starch molecule only at C-1. The structure of amylose is believed to be a succession of α-maltose residues, where the part between the dotted lines is repeated a large number of times.



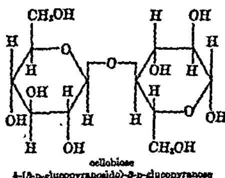
Starch in colloidal solution does not reduce hot Fehling's solution, does not react with phenylhydrazine, and is not fermented by zymase (p. 642). It is hydrolyzed by enzymes called amylases and by heating with acids. Hydrolysis proceeds through a succession of progressively less complex substances called **dextrins** to the final sugar, glucose, some of which is also being formed throughout the process. Maltose is an

glucosazone. This shows that the glucose part of the molecule is able to unite with phenylhydrazine, whereas the galactose part is not. This indicates that the free aldehyde group is in the glucose half. Other evidence indicates that lactose is a β-galactoside, not an α-galactoside. The union is with the fourth carbon atom of the glucose half. Lactose is thus a galactosidoglucose.



lactose
4-(β-D-galactopyranosido)-β-D-glucopyranose

Cellobiose, $C_{12}H_{22}O_{11}$. This is obtained by the hydrolysis of cellobiose octaacetate. The latter compound is formed when cellulose stands for several days with acetic anhydride in the presence of concentrated sulfuric acid. This treatment causes a gradual breakdown of the cellulose molecule and simultaneous acetylation of the fragments. Cellobiose is of interest because it is believed to be the unit from which the cellulose molecule is built. Cellobiose is cleaved by emulsin and is therefore a β-glucoside. The union is with the fourth carbon atom. As isolated, cellobiose is a β-sugar. It is a glucosidoglucose. Cellobiose differs from maltose in being a β-glucoside, whereas maltose is the isomeric α-glucoside.



cellobiose
4-(β-D-glucopyranosido)-β-D-glucopyranose

Trisaccharides. Of the many sugars of this class the most important member is raffinose, which is found along with sucrose in the sugar beet. When hydrolyzed, it yields glucose, fructose, and galactose.

POLYSACCHARIDES

cording to the needs of the plant. Starch is stored in the seeds in order that the young

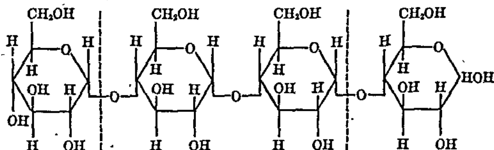
plant of the next generation may have a supply of food until able to shift for itself, and cellulose is a component of the framework of the plant. Or glucose may be converted to some other sugar and this may form the building unit, *e.g.*, mannose in mannan or xylose in xylan.

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intermediate product. Hydrolysis of starch to maltose has historically been accomplished by malt. This is barley that has been allowed to sprout, during which time there is a development of amylases commonly known as diastase. Then the barley is heated to stop the growth. The hydrolysis of starch to maltose is one step in the industrial process of beer making, which involves the conversion of maltose to alcohol by the enzymes of yeast (p. 642). Although maltose does not undergo fermentation by zymase, it is fermented by yeast because the enzyme, **maltase**, in malt, promotes the hydrolysis of maltose to glucose, a fermentable sugar (p. 642).

With free iodine, starch gives a characteristic blue color, which is intensified in the presence of iodide ion. The color is often used as an endpoint in iodimetry. The color fades on heating and returns on cooling.

The digestion of starch is accomplished partly by the saliva and finally by the pancreatic juice in the duodenum, through the action of amylases (p. 606). That of the saliva often is called **ptyalin**. As a result of these digestive processes starch is converted to glucose, which passes through the intestinal walls to the blood stream and by it is transported to all parts of the body.

Glycogen. This is sometimes called animal starch. It is found in the blood, in various organs, and especially in muscle and in the liver. Many fungi contain glyco- [illegible] [illegible] [illegible] not reduce Fehling's solution. Glycogen is converted by dilute acids and by diastase and ptyalin through dextrin and maltose to glucose.

Glycogen forms a readily available source of energy since in the body it is readily converted into glucose. When the glucose content of the blood drops below normal, the liver converts glycogen to glucose, and when it rises above normal following a meal, the excess is converted into glycogen.

Cellulose. This forms the cell walls of all plants and largely constitutes those parts where strength is required, such as branches, trunk, and roots. Wood, hemp, flax, cotton fiber, etc., are mainly cellulose, and the last named is comparatively pure cellulose. Besides cellulose, wood contains lignin, which has a free aldehyde group and can be dissolved by treatment with many reagents, such as caustic alkalies, sulfides, and bisulfites of the alkali and alkaline earth metals, and sulfur dioxide. The pure cellulose left behind is used in paper making.

Cellulose is a more stable and resistant polysaccharide than starch. It is insoluble in hot and cold water. It does not reduce Fehling's solution or show any of the reactions of an aldehyde group. Cellulose is hydrolyzed when heated with mineral acids, and the final product is glucose. This operation is usually performed under pressure in order to attain sufficiently high temperatures. Glucose is sometimes obtained this way for fermentation purposes. Cellulose contains three hydroxyl groups for every six carbon atoms and can be converted to esters and ethers. Cellulose dissolves in

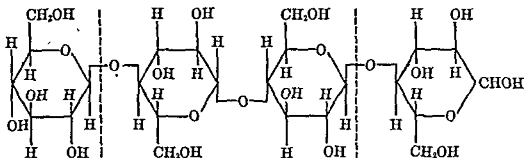
$$\underset{\text{cellulose triacetate}}{[C_6H_7O_2(OCOCH_3)_3]_n} \qquad \underset{\text{cellulose trinitrate}}{[C_6H_7O_2(ONO_2)_3]_n} \qquad \underset{\text{trimethyl cellulose}}{[C_6H_7O_2(OCH_3)_3]_n}$$

ammoniacal cupric hydroxide (Schweitzer reagent), probably because of the formation of complex copper compounds at the hydroxyl groups. Like alcohols, cellulose also forms a xanthate with sodium hydroxide and carbon bisulfide.

$$C_2H_5OH + CS_2 + NaOH \longrightarrow C_2H_5OCSSNa + H_2O$$

$$\underset{\text{cellulose}}{CelOH} + CS_2 + NaOH \longrightarrow \underset{\text{cellulose xanthate}}{CelOCSSNa} + H_2O$$

Molecular weight determinations have been made by the sedimentation equilibrium method (p. 603) on a cuprammonium solution of cellulose and on cellulose nitrate and cellulose acetate in acetone. Those made from purified cotton linters gave values ranging from 100,000 to 300,000. The structure of cellulose is believed to be a succession of cellobiose units, where the part between the dotted lines is repeated a large number of times.



***Cellulose nitrates** are obtained by the action of a mixture of nitric and sulfuric* acids upon cellulose and are commonly but incorrectly called **nitrocellulose.** These nitrates are esters, and the maximum degree of esterification (commonly called nitration) is reached when there are three nitrate radicals for every glucose unit. The degree of nitration is indicated by the percentage of nitrogen, the highest value of which is 14.17 per cent. However, this is seldom reached.

Smokeless powder is cellulose nitrate having a nitrogen content of 12.5 to 13.5 per cent. It closely resembles ordinary cotton in appearance but when dry is rapidly inflammable. It will swell or gelatinize when in contact with a mixture of alcohol and ether or mixtures of other organic solvents. In this gelatinized condition it can be fashioned into a variety of forms such as granules, cords, and strips, which retain their shape during removal of the volatile liquids. The resulting product is hornlike in appearance, will burn slowly when ignited in the open, and will explode when ignited in a closed space. **Cordite,** which is made from cellulose nitrate, glycerol nitrate, vaseline, and acetone, is used extensively as a propellant.

Pyroxylin is a lower nitration product (10.5–12.5% N). It is used in large quantities. It forms the basis of nitrocellulose lacquers. These are solutions of pyroxylin, a plasticizer, and some dye in a suitable solvent, usually butyl acetate mixed with one or more other organic liquids. Many plastic materials are made from pyroxylin by the addition of a plasticizer. One of the best known of these, and historically the first important industrial plastic, is **celluloid,** made with camphor, alcohol, and pigments. Another plastic is called pyralin. Celluloid and pyralin are thermoplastic and can be molded to desired shapes by pressure and heat. Cellulose nitrate was the original base for photographic films. **Collodion** is an alcohol-ether solution of a lower cellulose nitrate. On evaporation of the solvent the nitrate remains as a flexible film.

Cellulose acetate is made by acetylating cellulose with acetic anhydride in the presence of a catalyst, usually sulfuric acid, sometimes zinc chloride. Cellulose acetate is an important industrial product. It is soluble in many organic solvents, and on evaporation of the solvent the cellulose acetate is left behind as a flexible film. It burns with difficulty and on that account is superior to cellulose nitrate for many purposes, especially in photographic films. Cellulose acetate can be made into threads from which fabrics can be woven. These have an appearance of silk. Safety glass is made by subjecting to high pressure two sheets of glass with a sheet of cellulose acetate between them.

Rayon is cellulose which has been forced through small tubes while in a dissolved state and then reprecipitated from solution in the form of fine threads. These threads are spun into heavier ones, and from them various fabrics are constructed. Cellulose may be put into solution by one of three methods; (*a*) conversion to a nitrate and solution of this in a suitable organic solvent; (*b*) dissolution in cuprammonium solution; (*c*) conversion to soluble alkali xanthate. The last method, called the viscose process, has largely superseded the other two, which are now mainly of historical interest. The cellulose xanthate is obtained as a highly viscous mass, which is forced under pressure through small tubes and the resulting fine threads enter an acid bath. The acid causes decomposition of the xanthate with generation of cellulose in the form of fine threads The cellulose threads obtained in this way have a silklike luster which makes rayon more attractive than ordinary cotton goods. In the nitrocellulose process the nitrate groups are converted into hydroxyl groups by reduction. Cellophane is made in the same way as rayon except that the material is extruded through narrow slits rather than through small openings.

Yeast Fermentation. This fermentation takes place when fruit juices are allowed to stand for some time. Fermented liquids, mainly wine, from grapes, have been known since ancient times The juice becomes contaminated with yeast, a microorganism of the vegetable world, the most useful type of which is *Saccaromyces*. Some varities can change a number of sugars to alcohol, for example, sucrose, maltose, glucose, fructose, and mannose.

Buchner's proof that alcoholic fermentation could take place in the absence of living yeast cells disproved an early belief that alcohol was a metabolic product of the yeast cell, and showed that the conversion of sugar into alcohol and carbon dioxide is independent of the life processes of the yeast cell. He ground yeast cells and sand together and subjected the mixture to high pressure. The liquid pressed out was filtered free of yeast cells, and when added to a sugar solution, produced fermentation. The active material (an enzyme) was thus shown to have an existence outside of the cell and to be effective, even when no yeast cells were present.

The enzyme that produces alcoholic fermentation is called zymase. Actually it is not a single substance, but two. The one now called zymase is a protein, and the other, now-called co-zymase, is derived from diphosphoric acid, D-ribose, adenine, and nicotinamide. The two together do not ferment all sugars; no sugar which is not a monosaccharide and does not have either three or a multiple of three carbon atoms is fermented. Of the sugars containing the requisite number of carbon atoms, many are not changed. The sugars that are readily fermented are D-glucose, D-fructose, and D-mannose. Less readily fermented are dihydroxy acetone, glyceric aldehyde, D-galactose, and D-mannononose. It appears that the configuration of the sugar is of prime importance. Of the sixteen aldohexoses and eight 2-ketohexoses only four are fermented, and three of these, D-glucose, D-mannose, and D-fructose, have the same configuration on the third, fourth, and fifth carbon atoms. Their antipodes, L-glucose, L-mannose, and L-fructose are not affected

Yeast causes, in dilute aqueous solution, the alcoholic fermentation of many sugars that are not changed by zymase. This is because yeast contains other enzymes that change other sugars into fermentable monosaccharides; it contains invertase, which inverts sucrose; also maltase, which hydrolyzes maltose to glucose and splits α-glucosides into glucose and alcohols.

Starch and cellulose are unfermentable. However, starch is used for the production of beer and ale. It is converted first to maltose by the action of malt (p. 640)

and then to alcohol by yeast. Cellulose can serve as a source of alcohol after it has undergone hydrolysis to glucose.

PROBLEMS

1. Write the acyclic structure of:

a) an aldotetrose
b) a ketotriose
c) a 2-ketopentose
d) a 3-ketohexose
e) an aldoheptose
f) an aldooctose
g) a 2-ketoheptose
h) a 3-ketoheptose

2. What product would be expected from galactose by a reaction with:

a) propionic anhydride (5 moles)
b) *p*-bromobenzoyl chloride (5 moles) and pyridine
c) benzenesulfonyl chloride (5 moles) and pyridine
d) *p*-toluenesulfonyl chloride (5 moles) and pyridine
e) ethyl iodide (5 moles) and silver oxide
f) benzyl chloride (5 moles) and silver oxide
g) sodium amalgam and water
h) hydrogen cyanide
i) phenylhydrazine (1 mole)
j) phenylhydrazine (3 moles)

3. For the compounds listed below calculate from the data of the tables the relative proportions of the reactive species that would be present at equilibrium, on the assumption that only those compounds listed in the tables are involved in the equilibrium.

a) galactose
b) glucose
c) lyxose
d) mannose
e) talose
f) gluconolactone
g) maltose
h) lactose

4. Starting with D-galactose (aldehydo structure) show the steps involved in preparing:

a) dulcitol
b) D-galactonophenylhydrazide
c) D-talose
d) D-galacturonic acid
e) D-lyxose
f) a 2-ketohexose

5. Write the configuration of:

a) pentaacetyl-α-D-glucopyranose
b) pentapropionyl-β-D-glucopyranose
c) 2,3,6-trimethyl-α-D-glucopyranose
d) 6-triphenylmethyl-β-D-mannopyranose
e) tetramethyl-β-D-fructopyranose
f) tetraethyl-α-D-fructofuranose
g) ethyl α-D-glucopyranoside
h) benzyl β-D-glucopyranoside
i) ethyl β-D-glucofuranoside
j) methyl tetramethyl-α-D-glucopyranoside
k) ethyl tetramethyl-β-D-glucofuranoside
l) methyl 2, 3, 6-triethyl-β-D-galactopyranoside
m) methyl tetramethyl-α-D-galactopyranoside
n) methyl tetraacetyl-α-D-glucopyranoside
o) ethyl 6-benzoyl-β-D-galactopyranoside

p) ethyl α-D-fructopyranoside
q) benzyl β-D-fructofuranoside
r) methyl trimethyl-α-L-arabinopyranoside
s) methyl tetramethyl-β-D-fructopyranoside
t) methyl tetramethyl-α-D-fructofuranoside

6. Starting with D-mannose (aldehydo configuration) show the *steps* involved in preparing:

a) D-mannonolactone
b) D-mannitol
c) D-*manno*-saccharic acid
d) D-mannose phenylhydrazone
e) D-mannuronic acid
f) D-mannonophenylhydrazide
g) D-mannose phenylosazone
h) D-fructose
i) D-ribose
j) D-*arabo*-trihydroxyglutaric acid

7. Starting with α-D-mannose, show the steps to be followed in preparing the following, and give its configuration:

a) pentaacetyl-α-D-mannopyranose
b) D-mannonic δ-lactone
c) methyl tetramethyl-α-D-mannopyranoside
d) D-mannonic γ-lactone

8. By means of balanced equations showing configurational formulas and the actual reagents, give the steps involved in the preparation of the following from α-D-xylopyranose:

a) D-xylonolactone
b) xylitol
c) *xylo*-trihydroxyglutaric acid
d) tetrabenzoyl-α-D-xylopyranose
e) methyl β-D-xylopyranoside
f) ethyl triethyl-α-D-xylopyranoside
g) D-xylosone
h) D-*arabo*-trihydroxyglutaric acid
i) DL-xylonolactone
j) β-D-lyxopyranose
k) D-xylonophenylhydrazide
l) D-arabitol
m) D-gulono-γ-lactone
n) L-*gluco*-saccharic acid
o) D-gulose
p) methyl triacetyl-α-D-xylopyranoside

9. Describe a convenient chemical test (reagent, conditions, solvent if any, and readily detectable change) that serves to distinguish between:

a) glucose and sorbitol
b) glucose and gluconic γ-lactone
c) glucose and glucuronic acid
d) glucose and mannose
e) mannose and mannitol
f) mannose and methyl mannoside
g) mannose and pentaacetylmannose
h) mannose and mannuronic acid
i) mannose and fructose
j) mannose and galactose
k) galactose and dulcitol
l) galactose and arabinose
m) galactose and galacturonic acid
n) galactose and fructose
o) galactose and pentamethylgalactose
p) galactonic acid and mucic acid

10. Compound *A*, $C_6H_{12}O_6$, reduces Fehling's solution and is optically active. Bromine [illegible]

[illegible]

What conclusions can be drawn from these statements? Show how a structure and a configuration of *A* can be deduced. Are other configurations possible?

11. Compound *A*, $C_5H_{10}O_5$, reduces Fehling's solution and is optically active. By the action of bromine (1 mole) in aqueous solution compound *B*, $C_5H_{10}O_6$, optically active, is obtained. With calcium hydroxide this gives *C*, $C_{10}H_{18}O_{12}Ca$. With hydrogen peroxide and ferric acetate *C* is converted to *D*, $C_4H_8O_4$, also optically active. Oxidation of this gives dextrorotatory tartaric acid. What deductions can be drawn from these statements? Show how a structure and configuration for *A* can be deduced.

12. Compound *A*, $C_6H_{12}O_6$, is optically active and reduces Fehling's solution. In aqueous solution *A* yields *B*, $C_6H_{10}O_6$, levorotatory, with bromine, and *C*, $C_6H_{14}O_6$, optically inactive, with sodium amalgam. By the Wohl degradation *A* yields *D*, $C_5H_{10}O_5$, optically active, and this yields *E*, $C_5H_{10}O_6$ with aqueous bromine. When heated for a long time with pyridine, this yields *F*, $C_5H_{10}O_6$. When *E* and *F* are separately heated with nitric acid, they respectively yield *G* and *H*, $C_5H_8O_7$; *G* is optically active, *H* is inactive. What deductions can be drawn from these statements? Show how they lead to a configuration of *A*.

13. Compound *A*, $C_{12}H_{22}O_{11}$, by complete methylation is converted into compound *B*, $C_{20}H_{38}O_{11}$. When *B* is heated for some time with dilute hydrochloric acid, two compounds are obtained, 2,3,4,6-tetramethyl-D-glucopyranose and 2,3,6-trimethyl-D-mannopyranose. Assuming no change in ring structures during the reactions, indicate the possible configurations that *A* and *B* may have.

CHAPTER 43

Terpenes and Camphors

Terpenes are hydrocarbons conforming to the general formula $(C_5H_8)_n$. They and numerous related oxygenated compounds are widely distributed in plants. They are present mainly in leaves, flowers, and fruits, sometimes in the wood (camphor wood, sandalwood). They are important constituents of the great majority of essential oils. As a rule these oils are separated from the plant by steam distillation or by extraction with a suitable volatile solvent (p. 507).

The function of terpenes in flowers is believed to be the attraction of insects. The function in leaves may be to act as a repellent to insects, or they may be only waste products. The function in roots may be germidical.

Terpenes are classified in groups: (1) hemiterpenes, C_5H_8, of which isoprene is the sole member (p. 90); (2) terpenes proper, $C_{10}H_{16}$; (3) sesquiterpenes, $C_{15}H_{24}$; and (4) polyterpenes, $(C_{10}H_{16})_n$. These last include diterpenes, $C_{20}H_{32}$, triterpenes, $C_{30}H_{48}$, and more complicated substances, of which natural rubber (p. 90) is the most important. This chapter is devoted mainly to the $C_{10}H_{16}$ group, and of these only a few of the more important terpenes and related oxygen compounds will be included.

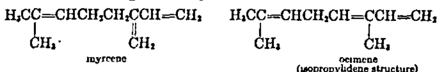
Isoprene, C_5H_8. This was described earlier (p. 90). It is mentioned again here because the carbon skeleton of a great many terpenes and derivatives thereof may be regarded as built up of isoprene units.

General Characteristics of Terpenes, $C_{10}H_{16}$. The terpenes are mostly colorless liquids (camphene is a solid), boiling in the temperature range of 150 to 180° and distilling with steam. Most have pleasant odors and many possess optical activity. They are unsaturated and show the characteristic reactions of olefins, for example, polymerization, addition of numerous reagents such as chlorine, bromine, hydrogen halides, nitrosyl chloride, and nitrogen dioxide, or formation of peroxides with air. Many undergo isomerization on the addition of acids. Mild oxidizing agents convert many to benzene derivatives, for example, iodine converts α-pinene to *p*-cymene. The terpenes are classified into the groups: (1) acyclic, (2) monocyclic, and (3) bicyclic.

ACYCLIC COMPOUNDS

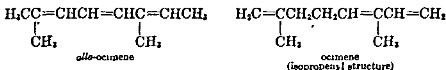
Hydrocarbons, $C_{10}H_{16}$. These are quite limited in number, and in comparison to cyclic terpenes are of minor importance. However, they are important from the standpoint of structure, because the carbon skeleton of most terpenes is related to that of myrcene, ocimene, and *allo*-ocimene.

Myrcene, 2-Methyl-6-methylene-2,7-octadiene. This occurs in bay oil (*Myrcia acris* D. C.), verbena oil, oil of hops, and other oils. Myrcene on pyrolysis is converted largely to isoprene.



Ocimene, 2,6-Dimethyl-2,5,7-octatriene. This occurs in the Javanese oil of *Ocimum basilicum* and other oils. Ocimene is particularly sensitive to oxygen. Just a short exposure to the air causes it to polymerize to a yellow resin, although it remains unaltered when oxygen is excluded.

***allo*-Ocimene, 2,6-Dimethyl-2,4,6-octatriene.** This is formed from ocimene when it is boiled for a few hours in a neutral atmosphere, or by pyrolysis of α-pinene. *allo*-Ocimene, on account of its conjugated system of three double bonds, polymerizes readily. It appears to have some promise in the production of useful polymeric materials



The structure of ocimene has been in dispute for some time, and it has been regarded as a mixture of the isopropylidine and isopropenyl forms From the infrared absorption spectrum of the purest specimens it is now believed to have the isopropylidine structure. This same uncertainty has existed with respect to a number of other compounds, for example, geraniol, citronellol, linalool, citral, and citronellal. These are now known to have the isopropylidene structure.

Carotene, $C_{40}H_{56}$. Although carotene is not a terpene, since its degree of unsaturation exceeds that of a terpene, and it is not acyclic, since it has two cyclohexene rings, it is mentioned here because its carbon skeleton can be regarded as made up of eight isoprene units and it has a long aliphatic chain. Carotene is the pigment responsible for the yellow color of carrots. There are three carotenes, *viz.*, α-, β-, and γ-carotene, all present in carrots. They can be separated by chromatography. The β-isomer is the most important of the three. The pure solid is dark red in color and yellow in very dilute solutions. The red color is the result of the long conjugated chain involving eleven double bonds (Fig. 34). The isomeric α-carotene differs in having the double bond of one cyclohexene ring located one carbon atom farther away from the CH group of the long carbon chain. The ring carbon attached to

the CH group in α-carotene is thus asymmetric, and α-carotene possesses optical activity.

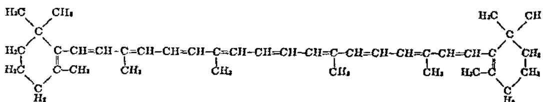
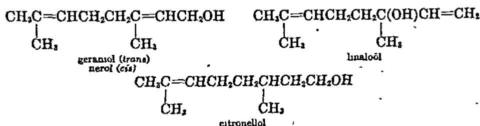


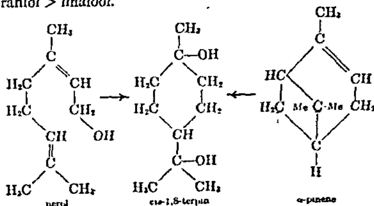
Figure 34 • β-**Carotene**

β-Carotene is called a provitamin because it is believed to precede the formation of vitamin A (p. 649). When carotene is given, in conjunction with vitamin D, to an animal suffering from vitamin A deficiency, the carotene effects are much the same as when good cod-liver oil is administered.

Alcohols. The important alcohols are those that are related to the terpenes as hydration products of the terpenes or partially hydrogenated terpenes. A number of these occur in plants. Geraniol, $C_{10}H_{17}OH$, occurs in oil of geranium, of which it is the main component (40–50%), oil of rose, oil of citronella, and many other oils. Nerol, $C_{10}H_{17}OH$, occurs in oils of neroli, rose, lavender, and others. Linaloöl, $C_{10}H_{17}OH$, occurs in linaloe oil and as the acetate in oils of bergamot and lavender. Citronellol, $C_{10}H_{19}OH$, occurs in oils of citronella, rose, geranium, and others. All of these alcohols have roselike or geraniumlike fragrance, and are widely used in the perfumery industry. They all have the carbon skeleton of myrcene or ocimene.

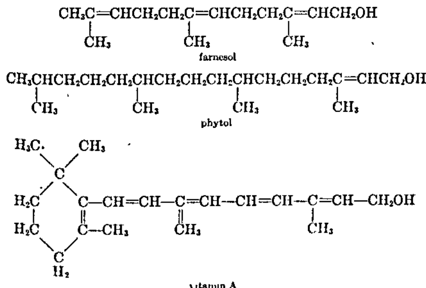


Geraniol, nerol, and linalool undergo cyclization when shaken with dilute (5%) sulfuric acid. The product is *cis*-terpin (1,8-terpin) in the form of a hydrate, *viz.*, terpin hydrate. The rates of cyclization are in the order: nerol > geraniol > linalool.



The cyclization is due to the addition of the alcoholic function (a reactive, allylic type) to the reactive double bond. This cyclization reaction shows that it is possible to pass from acyclic to cyclic terpenes or derivatives. This same terpin hydrate is produced by the hydration of α-pinene or turpentine oil (of which pinene is the main component), when it is shaken for a long time with 25 per cent sulfuric acid in an atmosphere of nitrogen or carbon dioxide.

Higher Alcohols. Three of these having carbon skeletons made up of isoprene units are farnesol, $C_{15}H_{25}OH$, phytol (phytyl alcohol), $C_{20}H_{39}OH$, and vitamin A, $C_{20}H_{29}OH$. Farnesol occurs in oil of rose, oil of citronella, neroli oil, and other oils. Phytol is present in chlorophyll as an ester and is liberated from combination when methanol is added. Vitamin A is found in cod-liver oil, shark-liver oil, and other fish-liver oils. Farnesol has one more isoprene unit than citronellol; phytol and vitamin A have still one more. The degree of saturation is different, and vitamin A has a cyclohexene ring.



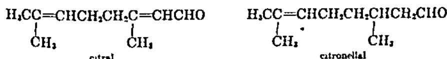
farnesol

phytol

vitamin A

Vitamin A is a growth-promoting vitamin. A deficiency leads to a lowered rate of growth, to night blindness, and to various eye lesions, such as xerophthalmia. Vitamin A is believed to be formed from carotene by the breaking of the molecule into two fragments at the center double bond through the addition of two molecules of water. The enzyme bringing about this change in the liver is called carotenase.

Aldehydes. The two principal aldehydes are citral and citronellal.



citral citronellal

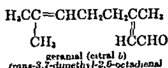
These bear the same relation to each other that geraniol and citronellol do, namely, citral is more unsaturated than citronellal. There are two isomeric

TABLE 109 | Some Terpenes and Related Compounds[a]

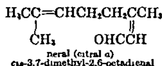
NAME	FORMULA	M.P. °C	B.P. °C	B.P. at mm.	d_4^{20}	n^{20} D	$[\alpha]_D$
(+)-Borneol	$C_{10}H_{17}OH$	208	212				+37 9
(+)-Camphene	$C_{10}H_{16}$	51.2	157 6	745	0.8462^{14}	1.4605^{14}	+107
(+)-Camphor	$C_{10}H_{16}O$	179.5	207	50	0.995		+44
Carotene-β	$C_{40}H_{56}$	187.5					
(+)-Citronellal	$C_9H_{17}CHO$		205–200		0.855	1 448	+12.30
(−)-Citronellol	$C_9H_{17}CH_2OH$		103–104	10	0 8562	1.4560	−4.2
Farnesol	$C_{14}H_{25}CH_2OH$		160	10	0.8871	1.4890	
Geranial (citral *a*)	$C_9H_{15}CHO$		118–119	20	0.8898	1.4894^{17}	
Geraniol	$C_9H_{15}CH_2OH$		229–230	757	0.883^{15}	1 4766	
			110–111	10			
(−)-Isoborneol	$C_{10}H_{17}OH$	217					−34
(+)-Limonene	$C_{10}H_{16}$		177.6–177.8	760	0.8403	1.4750	+126
(−)-Linaloöl	$C_{10}H_{17}OH$		198–199	760	0.870^{15}	1.4668	−20 7
(−)-Menthol	$C_{10}H_{19}OH$	43	216	760	0 9007	1 4609	−50 5
(−)-Menthone	$C_{10}H_{18}O$	−6	204	750	0 8946	1 4504	−29 60
Myrcene	$C_{10}H_{16}$		166–168	760	0.791	1 4650	
			72–73	25			
Neral (citral *b*)	$C_9H_{15}CHO$		117–118	20	0.8888	1.4891	
Nerol	$C_9H_{15}CH_2OH$		224–225	760	0.8813^{15}	1 462	0
			125	25			
Ocimene	$C_{10}H_{16}$		176–178	760	0.8031^{15}	1.4857^{15}	
			73–74	21			
Ocimene-*allo*	$C_{10}H_{16}$	A −21 to −20 6	89	20	0 8060	1 5446	
		B −35.4 to −34.0	91	20	0 8118	1 5446	
Phytol	$C_{19}H_{39}CH_2OH$		202	10	0.8462^{25}	1 4640	
			145	0 02			
(+)-Pinene-α	$C_{10}H_{16}$	−57	156–156.5	760	0 859	1 466	+51 8
(−)-Pinene-α	$C_{10}H_{16}$	−55	156–157	760	0.859	1 466	−51 2
Terpene-1,8-*cis*	$C_{10}H_{18}(OH)_2$	104–105[b]	258	760			
Vitamin A	$C_{19}H_{27}CH_2OH$	63–64	137–138	10^{-3}			

[a] Data mainly from *The Essential Oils* by E. Guenther, D Van Nostrand Co , Inc., New York, 1949, and *The Terpenes*, by J. L. Simonsen, University Press, Cambridge, Eng , 1947. [b] m p. of hydrate, 116–117°.

forms of citral, *viz.*, citral *a* (geranial), the *trans*-form, obtained by oxidation of geraniol, and citral *b* (neral), the *cis*-form, obtained by oxidation of nerol.



geranial (citral *b*)
trans-3,7-dimethyl-2,6-octadienal

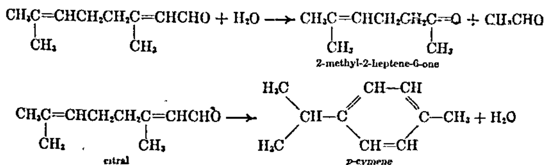


neral (citral *a*)
cis-3,7-dimethyl-2,6-octadienal

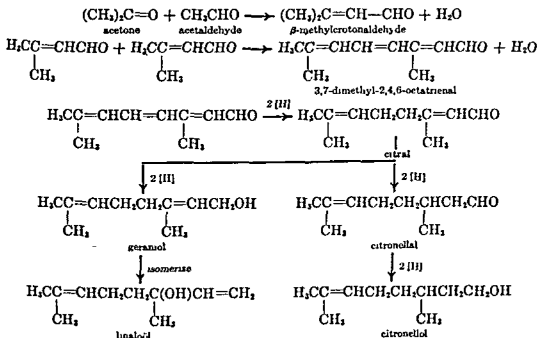
Citral occurs in a great many essential oils, for example, oil of lemon (6–7%), lime, citronella, and lemon grass (70–80%). It possesses a characteristic lemonlike flavor. Citronellal is found in oil of citronella, in some eucalyptus oils, and in Jeffrey pine oil. Both aldehydes are used extensively for the scenting of industrial products such as soaps, cosmetics, and perfumes; citral also is an ingredient of flavors, such as those of lemon and lime.

They undergo typical reactions of aldehydes (Chap. 17). Citral, like acrolein, reacts with two molecules of sodium bisulfite (p. 288). Citral undergoes two other important reactions. It undergoes scission, when heated in aqueous sodium carbonate, to acetaldehyde and 2-methyl-2-heptene-6-one, a re-

versal of the aldol condensation reaction (p. 272), and it cyclizes to *p*-cymene when heated with dilute sulfuric acid or potassium bisulfate.



The synthesis of terpenes in the plant is believed to proceed through geraniol or some similar alcohol, since the formation of cyclic terpenes proceeds readily from these. A much favored mechanism starts with acetone and acetaldehyde. It is hardly likely that these are present in the plant as such, but are probably in combination with some plant constituent, such as a sugar.



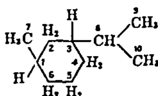
By an aldol type of condensation β-methylcrotonaldehyde would result from acetone and acetaldehyde and then, by a repetition of the process, yield an aldehyde having the *allo*-ocimene structure, in a manner analogous to the condensation of crotonaldehyde (p. 273). This aldehyde could be reduced in the plant to citral, and this in turn to geraniol or citronellal, depending on whether the reduction at the olefinic double bond proceeds via a 1,4- or a 1,2-mechanism. Isomerization of geraniol would account for the formation of linaloöl and further reduction of citronellal would account for citronellol.

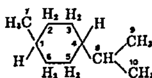
Condensation of the octatrienal with a third molecule of β-methylcroton-

aldehyde would give the carbon skeleton of farnesol, and with still another, would give that of phytol. Ring closures, similar to that of geraniol, could give rise to cyclic terpenes.

MONOCYCLIC TERPENES

The monocyclic terpenes, $C_{10}H_{16}$, have the carbon skeleton of either *m*-menthane (1-methyl-3-isopropylcyclohexane) or *p*-menthane (1-methyl-4-isopropylcyclohexane). Those having the *p*-menthane structure are much more important. Of these, limonene (dipentene) is the most important. Next to α-pinene it is the most widely distributed of all the terpenes.

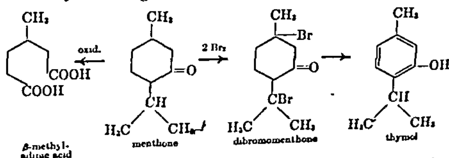

m-menthane


p-menthane

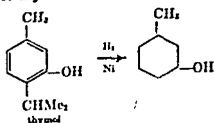
The menthanes, $C_{10}H_{20}$, are not terpenes and they are not found in nature.

Menthol, $C_{10}H_{19}OH$. This is present in peppermint oil, obtained from various species of *Mentha piperita* L. Menthol has a characteristic odor suggestive of camphor. It is a mild antiseptic and for this reason is an ingredient of many medicinal preparations. It produces a sensation of coolness when applied to the skin. Its presence in cigarettes is claimed to produce a cool smoke.

Menthol is an alcohol, for it can be converted to a monoacetate. Mild oxidation converts menthol to menthone, $C_{10}H_{18}O$, a ketone. The structure of menthone is established by its conversion to β-methyladipic acid on oxidation, and to thymol through dibromomenthone, by heating this with quinoline.


β-methyl-adipic acid menthone dibromomenthone thymol

The relation of menthol to thymol and menthane is established by hydrogenation of thymol to menthol, and conversion to men

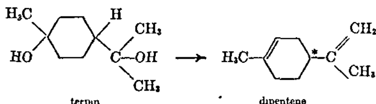

thymol

These reactions establish

Since *p*-menthane is $C_{10}H_{20}$ and the terpenes are $C_{10}H_{16}$, terpenes having this carbon skeleton must have two double bonds per molecule. Therefore they are menthadienes. The most important of this group is limonene (dipentene).

Dipentene and Limonene, $C_{10}H_{16}$, b.p. 178°. Limonene exists in *dextro-* and *levo-* forms; dipentene is a name given to inactive (racemic) limonene In its three forms limonene is one of the most widely distributed of the terpenes. The (+)-isomer is found in many oils, for example, oil of orange (*ca.* 90%), neroli, lemon, celery (*ca.* 60%), and caraway (*ca.* 40%); the (−)-isomer is found in pine-needle oil (from *Abies alba*) and in oil of fir, spearmint, and peppermint; dipentene is found in very many oils, for example, numerous turpentine oils, oil of lemon grass, citronella, pepper, and camphor.

Dipentene is obtained from a number of terpene alcohols when they are heated with dilute acids. A typical example is its formation from 1,8-terpin.



BICYCLIC TERPENES

There are a number of bicyclic ring structures that are characteristic of bicyclic terpenes, $C_{10}H_{16}$. The parent saturated hydrocarbons, $C_{10}H_{18}$, *viz.*, thujane, carane, pinane, camphane, isocamphane, isobornylane, and fenchane (Fig. 35), do not occur naturally. The method of numbering, taken from *Chemical Abstracts,* is in some cases different from historical methods.

The isopropyl group of menthane forms part of other ring systems in some of the bicyclic structures. In carane it is responsible for the cyclopropane ring; in pinane, for the cyclobutane ring; and in camphane, for the cyclopentane rings. In the camphane structure the isopropyl group is sometimes referred to as the camphane bridge.

Bicyclic terpenes have only one double bond in the molecule. Quite a number of bicyclic terpenes are found in plants; the most important of these is α-pinene. A very large number of oxygen compounds (alcohols and ketones, mainly) occur naturally; the most important of these are the alcohol, borneol, and the ketone, camphor.

α-Pinene, $C_{10}H_{16}$. This is the most widely distributed of the terpenes and is a component of most of the essential oils obtained from the Coniferae. The *dextro*-isomer is found in Greek and Russian turpentine oil, the *levo*-isomer in Spanish, Austrian, and American turpentine oil. These oils, composed mainly of α-pinene, have been used extensively as solvents, mainly in the paint and varnish industry. Of more interest to the chemist is the fact that pinene is the starting point in the synthesis of a number of compounds, for example, borneol, camphor, terpin, and terpineol.

thujane

carane

pinane

camphane

isocamphane

isobornylane

fenchane

Figure 35 · Bicyclic Ring Systems

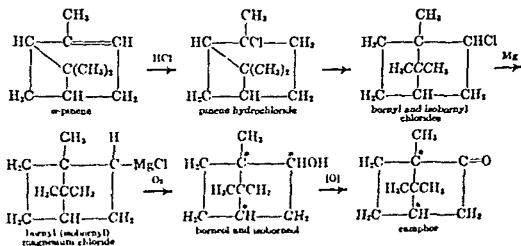


Figure 36 · Synthesis of Camphor from α-Pinene

In one of the earlier methods for synthetic camphor, pinene with hydrogen chloride yields pinene hydrochloride which, being unstable, rearranges to bornyl chloride (artificial camphor). This can be converted to the Grignard reagent with magnesium and the product undergoes oxidation with air to borneol. Borneol is readily oxidized to camphor (Fig. 36).

Other processes have been developed. In one of these an organic acid, for example, tetrachlorophthalic acid, is used in place of hydrogen chloride and the product, a bornyl ester, is saponified to borneol; in another method camphene is formed from the bornyl chloride by dehydrohalogenation with a base, and the hydrocarbon is converted to an isobornyl ester with a carboxylic acid, for example, isobornyl acetate with acetic acid; in a third method camphene is oxidized directly to camphor, but with a lower yield. The steps of different processes are shown in Figure 37.

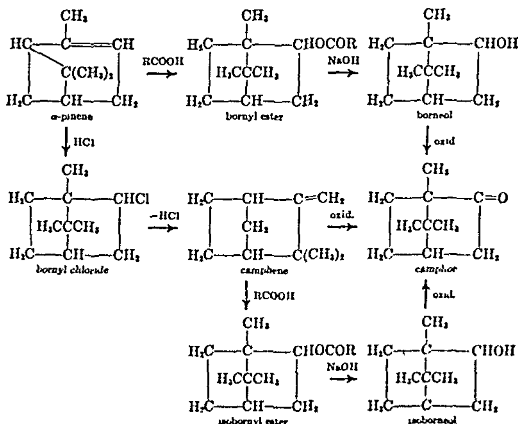


Figure 37 • Conversion of α-Pinene to Camphor

Borneol, 2-Camphanol, "Borneo Camphor," $C_{10}H_{17}OH$. This, an important terpene alcohol with a camphorlike odor, occurs rather widely distributed. The *dextro*-isomer is an important constituent of oils from varieties of *Dryobalanops*, trees of Borneo and Sumatra. The *levo*-isomer occurs in a number of oils, for example, citronella and yellow pine. Borneol is readily converted to a monoacetate, bornyl acetate. This has a typical pine-needle odor. By the action of numerous oxidizing agents, in particular, chromic acid, borneol is converted to camphor, and this, when

e) 2,5-dibromo-2-isopropyl-5-methylcyclohexanone
f) menthone oxime
g) *m*-menthane
h) 2-chlorocamphane
i) carane
j) pinane
k) fenchane
l) thujane

CHAPTER 44

Heterocyclic Compounds

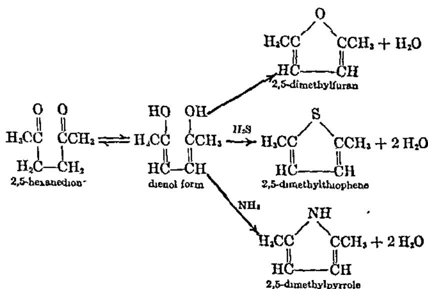
on • • . .

of atom. By fa the main division under homocyclic is the **carbocyclic** group, which comprises the cycloparaffin (including the terpene) and the aromatic series.

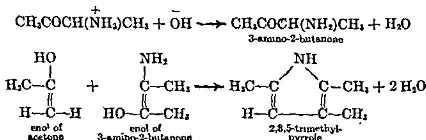
The atoms other than carbon that go to make up the rings of heterocyclic compounds are called hetero atoms. Nitrogen is the principal hetero atom, oxygen next, then sulfur. Phosphorus is becoming more important than formerly in this respect. Many compounds already described are heterocyclic. Among those having a hetero oxygen atom are epoxides, lactones, anhydrides of dibasic acids, and sugars; and among those having one or more hetero nitrogen atoms are lactams, imides of dibasic acids, and diketopiperazines. Most of these compounds have been described in connection with the acyclic compounds from which they are prepared and into which they usually can be converted readily. The most important heterocyclic compounds are aromatic. Most of the heterocyclic compounds described in this chapter have aromatic ring systems. The principal nonaromatic ring systems described here are those of pyrone, tetrahydrofuran, pyrrolidine, piperidine, and piperazine. The most important heterocyclic systems are those consisting of five-membered and six-membered rings.

There are two generally recognized ways of writing heterocyclic compounds, *viz.*, one showing the hetero atom at the bottom (the historical method, and the one followed by the majority of organic chemists); the other showing the hetero atom at the top (the one adopted by *Chemical Abstracts* for purposes of indexing). This text is in conformity with the latter. Numbering starts at the hetero atom and proceeds clockwise around the ring. In case there are two hetero atoms, oxygen takes preference over sulfur or nitrogen in the numbering, and sulfur over nitrogen. In an abbreviated type of formula only the hetero atoms appear. As in the case of benzene, hydrogen atoms are not shown, only single and double bonds. The other positions, if unsubstituted, are methine groups in the case of aromatic systems and methylene groups in the case of nonaromatic systems.

A diketone, for example, 2,5-hexanedione, with zinc chloride or sulfuric acid yields a dialkyl furan, with hydrogen sulfide, a dialkyl thiophene, and with ammonia, a dialkyl pyrrole.



Another method for pyrroles is the reaction of a ketone with an α-amino ketone, thus having two carbonyl groups and an amino group, equivalent to two carbonyl groups and ammonia in the reaction above. The amino ketone, being unstable, is formed by adding a base to one of its salts.

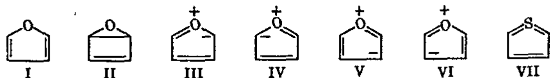


It is beyond the scope of this elementary text to describe other methods of ring closure.

Aromatic Character of Five-Membered Heterocycles. Furan, thiophene, and pyrrole are considered to be aromatic substances because they undergo some or all of the typical substitution reactions of benzene, such as halogenation, sulfonation, nitration, mercuration, the Friedel-Crafts reaction, the Reimer-Tiemann reaction, and diazo coupling. Some compounds, such as the pyrrols, are sensitive to acids and therefore cannot be sulfonated or nitrated under ordinary conditions. Pyrrole is the most reactive in electrophilic substitutions, next furan, and then thiophene. Furan has been referred to as being "superaromatic," to indicate its greater reactivity, relative to benzene. The greater reactivity of these compounds, as well as their aromatic character, is explained in terms of resonance.

The resonance forms of furan are shown as I, II, III, IV, V, and VI. These

are characteristic also of thiophene and pyrrole. The relative contributions of these forms to the complete structure of the furan molecule have been calculated from the dipole moment, the resonance energy, and the various interatomic distances by the methods of quantum mechanics.

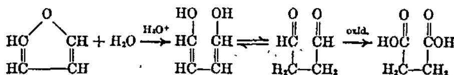


Form I contributes most to the complete structure, 80 per cent, II, 7 per cent, III and IV, 2.5 per cent each, and V and VI, 4.0 per cent each. The greater reactivity of furan in substitutions with electrophilic reagents, in comparison to benzene, is ascribed to the negative charges on the carbon atoms. It will be recalled that substituents that place negative charges on carbon atoms of the benzene ring greatly promote substitution (Chap. 28). One would expect, on the basis of the relative contributions of III, IV, V, and VI, that the β-position would be more reactive than the α-position. However, the contribution of II is also important because the long bond between the two α-carbon atoms is a weak bond, and substitution is promoted by the easy scission of this bond. The combination of II with III and IV makes the α-position of furan more reactive than the β-position. This relationship holds also for thiophene and pyrrole.

The resonance forms of pyrrole would be expected to be similar to those of furan, and those like III, IV, V, and VI would be expected to contribute more to the structure of pyrrole than is the case with furan, since nitrogen is less electronegative than oxygen and can acquire a positive charge more readily. Pyrrole undergoes substitution more readily than does furan. Thiophene is like furan, except its lower dipole moment points to an additional form, VII. This is somewhat like III, but differs in having no formal charge, as a result of expansion of the sulfur octet to accommodate the unshared electron pair on the α-carbon atom. As a result, the contribution of the dipolar forms, III to VI, is less. This is an explanation of the fact that thiophene is less reactive than furan.

The resonating character of these three heterocycles accounts for: (1) their aromatic character; (2) the order of reactivity, *viz.*, pyrrole > furan > thiophene > benzene; (3) the greater reactivity of the α-position over the β-position; and (4) the acidic and nonbasic character of pyrrole, a result of the positively charged nitrogen atom.

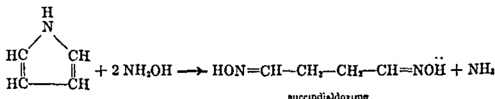
Ring Openings. Many five-membered aromatic heterocycles undergo ring opening with the proper reagents. Ring opening of the furan ring seems to be the easiest; this takes place with aqueous acids



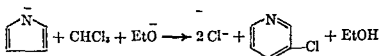
This is essentially the reverse of the ring closure of succinaldehyde. It is possible that the first product is the dienol, but this is not certain. If an oxidizing agent is present, then the aldehyde is oxidized to succinic acid. Usually the change is accompanied by extensive resinification with the result that yields are poor. In this ring opening, furan reacts like a vinyl ether, for vinyl ethers undergo hydrolysis readily. There are other reactions of furan that are explained best from the standpoint of a vinyl ether structure.

Thiophene undergoes ring opening when heated to 140° with hydriodic acid. Sulfur and hydrogen sulfide are formed. Also with alcoholic thallous hydroxide, thiophene is rapidly converted to thallous sulfide and succinic aldehyde. The latter is converted to succinic acid by oxygen in the air.

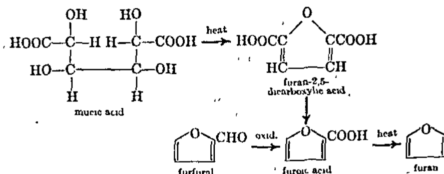
Pyrrole undergoes ring opening when heated in alcoholic solution with hydroxylamine, essentially a reversal of the ring closure, because the product is succindialdoxime.



Also, ring enlargement of pyrrole compounds sometimes takes place. As an example, β-chloropyridine is formed from N-pyrrolylpotassium, chloroform, and sodium ethoxide.



Furan, C_4H_4O. A source of furan, important historically, is furan-2,5-dicarboxylic acid, but the most important source is furfuraldehyde. The dibasic acid is formed when mucic acid (p. 617) is heated; on further heating furandicarboxylic acid decarboxylates first to furoic acid, then to furan. Also, furfuraldehyde is converted to furoic acid, which on decarboxylation yields furan.

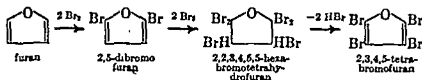


Furan brominates (in carbon tetrachloride solution) to 2,5-dibromofuran. This product with bromine gives 2,2,3,4,5,5-hexabromotetrahydrofuran by

TABLE 110 | Some Heterocyclic Compounds

NAME	M.P. °C	B.P. °C	NAME	M.P. °C	B.P. °C
Benzothiophene	32	221–222	γ-Picoline		144
Carbazole	245	355	Picolinic acid	137	
Chromone	59		Piperazine	104	146
Coumarin	67	301.7	Piperidine	−9	106.0
Coumarone	<−18	173–175	Pyrazine	54	117
Furan	−29.8	32	Pyrazole	70	186
Furfuraldehyde	−36.5	161.7	Pyridazine	−8	208
Furfuryl alcohol		171	Pyridine	−42	115.4
Furoic acid	134.3	230–232	Pyrimidine	22	124
Imidazole	90	256	α-Pyrone	+5	206–207
Indole	53	254	γ-Pyrone	32.5	216
Indoleacetic acid	164–165		Pyrrole		130
Isonicotinic acid	305–307		Pyrrolidine		88
Isoquinoline	24.8	243 .3	Quinoline		238.0
Isoxazole		95.5	Tetrahydrofuran	−108.5	65.7
Nicotinic acid	230–232		Thiazole		116.8
α-Picoline	−64	128	Thiophene	−40	87
β-Picoline		143.5	Xanthone	174	371

addition. Action of alkali converts the last to 2,3,4,5-tetrabromofuran. These changes show the tendency of furan to undergo addition, as well as substitution.



Other substitution products obtainable from furan are furan-2-sulfonic acid, with pyridine-sulfur trioxide; α-nitrofuran, with acetyl nitrate; α-acetylfuran, with acetic anhydride and a mild catalyst, such as zinc chloride or orthophosphoric acid; furfural, with hydrogen cyanide and hydrogen chloride; and α-furylsodium, with a sodium alkyl. Strong acids, such as nitric and sulfuric acids, and strong catalysts, such as anhydrous aluminum chloride, must be avoided, owing to the sensitivity of furan. If a negative substituent is attached to the furan ring, as for example a carbethoxy group, the molecule is more stable and can be subjected to more vigorous treatment. Also, bromine addition compounds are more stable and can be isolated.

The furan ring can be reduced to the ring system of tetrahydrofuran. Hydrogenation with a palladium–palladious oxide catalyst gives very good yields.

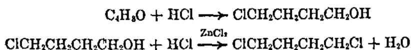
Furfuraldehyde, furfural, $C_5H_4O_2$. This distils over quantitatively and mixed with water when a pentose or a pentosan is heated vigorously with 12 per cent hydrochloric acid saturated with salt, so as to obtain a rapid distillation. Furfural shows the usual reactions of aldehydes and also those of

aromatic compounds. In substitution it is less reactive than furan. The principal industrial uses of furfural are the manufacture of thermosetting plastics, similar to those produced with formaldehyde, by reactions with phenols, urea, etc., and the production of tetrahydrofuran, an intermediate in the manufacture of nylon.

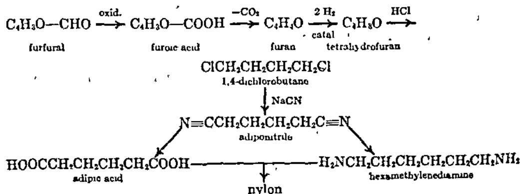
Furfural can be determined quantitatively by means of color reactions with a number of substances, in particular, aniline or phloroglucinol. Thus pentoses and pentosans also can be determined quantitatively.

Tetrahydrofuran, C_4H_8O. The principal method of production is reduction of furan. It can be formed from 1,4-butanediol by heating the latter with dilute sulfuric acid, conditions for ether formation (see Dioxane, p. 243). A recently developed industrial process for tetrahydrofuran starts with acetylene and formaldehyde. When these are heated to 100° under a pressure of 5 atmospheres, 2-butyne-1,4-diol is formed and catalytic hydrogenation of this gives 1,4-butanediol. This is converted to tetrahydrofuran by heating to 270° with a small amount of phosphoric acid.

Tetrahydrofuran is converted into 4-chloro-1-butanol (tetramethylene chlorohydrin) by passing anhydrous hydrogen chloride into the boiling liquid up to 106°, and to 1,4-dichlorobutane if some zinc chloride is added and additional hydrogen chloride is passed in.



Hydrogen bromide and hydrogen iodide convert tetrahydrofuran readily to 1,4-dibromobutane and 1,4-diiodobutane, respectively. The reaction with hydrogen chloride is an important industrial operation in connection with nylon manufacture. The dichloride is converted into the dicyanide, and this in turn is converted partly to adipic acid and partly to hexamethylenediamine (p. 394), as indicated in the following steps.



Thiophene, C_4H_4S. This is present in coal tar. It is found in the benzene fraction, of which it constitutes about 0.5 per cent. Homologs of thiophene are present in toluene and in other hydrocarbons obtained from coal

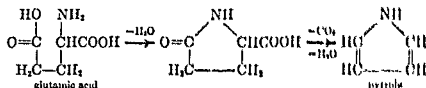
tar. In addition to methods already described (p. 650), thiophene may be formed by heating sodium succinate with "phosphorus trisulfide" (obtained by heating a mixture of phosphorus and sulfur, two parts to three).

Thiophene undergoes the usual substitution reactions of aromatic compounds, viz., halogenation, sulfonation, nitration, mercuration, acylation, and alkylation — the last with an alkyl halide, a secondary or tertiary alcohol or an alkene, the catalyst being stannic chloride, titanium chloride, zinc chloride, or other mild catalyst. In reactivity, thiophene lies between benzene and furan. As in the case of furan the α-position is the more reactive one, but not so outstanding, because some β-isomer may also be formed. Sulfonation with concentrated sulfuric acid at room temperature can be used for removing thiophene from benzene, because the thiophenesulfonic acid formed dissolves in the sulfuric acid phase, whereas benzene is little affected. From the acid phase thiophene is recovered by the following operations: dilution with water, precipitation of sulfuric acid with lead carbonate, conversion of the soluble lead salt of thiophenesulfonic acid to the ammonium salt, and heating this.

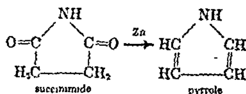
Another method of removing thiophene from benzene is based on the formation of an insoluble mercuric compound, thiophene dimercurihydroxyacetate, $C_4H_2S(HgOAc)HgOH$, when crude benzene is heated with aqueous acetic acid and mercuric oxide. Thiophene can be regenerated from this when it is heated with hydrochloric acid.

Thiophene gives an intense blue color when shaken with concentrated sulfuric acid containing a small amount of dissolved isatin (p. 670). This color reaction, the so-called indophenine test, was believed at one time to be a test for benzene, until Victor Meyer showed it to be due to thiophene.

Pyrrole, C_4H_5N. This is present in coal tar and in bone oil, the disagreeable volatile oil obtained from bones when they are heated sufficiently. This oil also contains homologs of pyrrole. Pyrolysis of other organic material, for example bran, also yields pyrrole. Pyrrole is believed to come from the glutamic acid residues of protein. When bran is being pyrolyzed, addition of chalk or barium hydroxide increases the yield of pyrrole, presumably because decarboxylation of an intermediate acid is promoted by the formation of an alkaline earth salt.

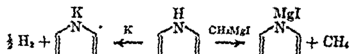


Pyrrole and pyrrole homologs can be synthesized by a number of ring closure methods, two of which have been mentioned (pp. 650, 660). It is conveniently prepared by pyrolysis of ammonium mucate or ammonium saccharate, a reaction paralleling the formation of furan from mucic acid (p. 662). If ammonia is replaced by an amine, the product is 1-alkylpyrrole. synthesis of pyrrole is from succinimide when it is heated with zinc

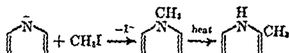


Pyrrole is a colorless liquid, sparingly soluble in water or in dilute aqueous acid or base, miscible with alcohol, ether, or other usual organic solvent. Its low solubility in dilute mineral acids indicates a lack of basic properties. In contact with strong acids it undergoes polymerization. Pyrrole gives the so-called pine-splinter test. A pine splinter, moistened with hydrochloric acid, is exposed to the vapor of the substance being tested. Pyrrole and many alkylpyrroles cause a pale red color that changes to a carmine red (Gr. *pyrros*, fiery red). Other substances may give a positive test, for example, indoles, and methyl homologs of furan.

Pyrrole forms pyrrolylpotassium when in contact with metallic potassium and ligroin, and forms pyrrolylmagnesium iodide with methylmagnesium iodide.



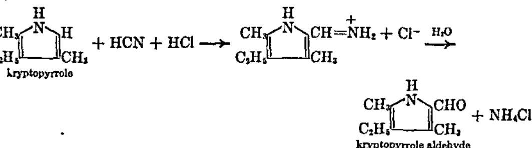
The formation of these compounds shows that pyrrole has the properties of an acid. The acid properties are weak, however, because the compounds are decomposed when added to water. The potassium salt is converted to N-methylpyrrole by methyl iodide.



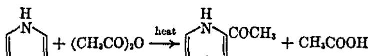
1-Methylpyrrole when passed through a hot tube yields 2-methylpyrrole, besides other products. Pyrrolylmagnesium iodide reacts with methyl iodide and the methyl radical goes to ring carbon; in this case the main product, however, is 3-methylpyrrole. Higher alkyl iodides give 2-alkylpyrroles. Pyrrolylmagnesium iodide readily undergoes acylation, in ether solution, with esters, anhydrides, and acyl halides, to form α-acylpyrroles.

Pyrrole undergoes substitution with electrophilic reagents very readily. It is more reactive than furan, and about as reactive as phenol. The explanation of its easy substitution is made on the basis of resonance forms (p. 661). The principal reactions are those of halogenation, alkylation, acylation, and azo coupling. Nitro and sulfo groups cannot be introduced with acids, owing to the sensitivity of pyrroles to acids. The usual reagent in chlorinations is sulfuryl chloride; α-chloropyrrole is formed first. Bromine gives 2,3,4,5-tetrabromopyrrole, and iodine in the form of triiodide ion gives 2,3,4,5-tetraiodopyrrole (iodole). This last reaction emphasizes the great reactivity of pyrrole.

Formyl groups are introduced with anhydrous hydrogen cyanide and hydro-
n chloride (Gattermann synthesis, p. 499), or with anhydrous zinc cyanide
place of hydrogen cyanide.

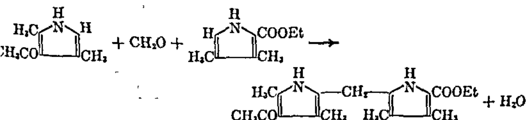


Carbonyl groups can be introduced into the pyrrole ring with an organic
itrile, RC≡N, in place of hydrogen cyanide, above. If both α-positions are
ccupied, the Friedel-Crafts reaction of an anhydride with aluminum chloride
cylates the β-position. Heating pyrrole with acetic anhydride alone gives
-acetylpyrrole.



Pyrrole even couples with diazonium salts, to yield azo pyrroles. Coupling
akes place preferentially at the α-position; if these are blocked, then at the
-position. Pyrrole itself gives a monoazo dye under basic conditions, but
nany homologs react twice under basic conditions.

An important group of pyrrole compounds are pyrryl derivatives of meth-
ne. These are formed by different condensation reactions, of which the fol-
owing is an example.



n this reaction only a dipyrrylmethane is formed, but with chloroform and
base, as in a Reimer-Tiemann reaction, a tripyrrylmethane is formed.
Vhen both α-positions are open and with the proper reagents, four pyrrole
esidues can be linked through methine groups to give porphyrins.

Pyrrole is important in connection with hemoglobin and chlorophyll. Both
f these have a remarkably similar grouping of four pyrrole rings in a porphy-
in. The two main chemical differences between hemoglobin and chlorophyll
re: hemoglobin contains iron, chlorophyll contains magnesium; hemoglobin
s a conjugated protein, chlorophyll is an ester and yields methyl and phytyl
lcohols on hydrolysis.

Hemoglobin. This is the red-colored protein of the blood of vertebrates. It has the property of combining loosely with oxygen, which is thus transported from the lungs to various parts of the body in the form of **oxyhemoglobin.** Hemoglobin contains iron in the ferrous state. This is involved in the oxygen absorption. One oxygen molecule is absorbed for each iron atom. In this process the color changes from purple, the color of venous blood, to red, the color of arterial blood. Carbon monoxide forms a more stable combination with hemoglobin than oxygen does and because of this will destroy the ability of hemoglobin to combine with oxygen. This is the cause of carbon monoxide poisoning.

Hemoglobin is a conjugated protein composed of globin and the prosthetic group, heme. Globin is colorless, heme is a deep red.

Heme, $Fe[C_{32}H_{30}N_4](COOH)_2$. When oxyhemoglobin is heated under controlled conditions with acetic acid containing sodium chloride it is cleaved into colorless globin and black **hemin.** Hemin contains iron in the ferric state Reduction of hemin by means of formic acid and iron filings removes the iron entirely and forms **protoporphyrin,** a purple compound, which is the real pigment. Gentle reduction of ferric iron to ferrous iron in hemin produces heme, which can be recombined with undenatured globin to produce a synthetic hemoglobin. This appears to be identical with the natural product. The structure of heme (Fig. 38) has been established, due largely to the brilliant researches of Hans Fischer.

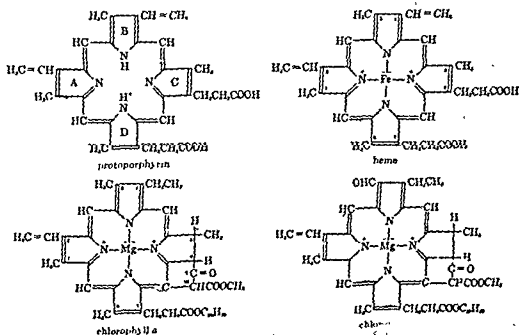


Figure 38 • Protoporphyrin, Heme. Ch... and Ch...

In the molecules of protoporphy... rings, *A*, *B*, *C*, and *D*, joined to one ano... carbon atoms. There is a closed c...

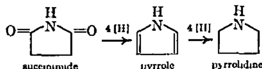
bonds in each molecule and this has the effect of increasing the stability of the systems, similar to the effect of the two Kekulé forms on the stability of benzene. In heme, ferrous iron replaces the two acidic hydrogen atoms of two pyrrole units of protoporphyrin, and it also coordinates with the other two nitrogen atoms. Thus it forms a covalent bond with each of the four nitrogen atoms. These bonds become equivalent through resonance. It is possible to write a number of resonance forms for heme and protoporphyrin and still have a completely conjugated system.

Ferrous iron has a coordination number of six. In oxyhemoglobin there are four coordinate links to the four nitrogen atoms, one to some atom of the globin molecule, and one to the oxygen atom.

Chlorophyll. Chlorophyll is the green pigment in leaves It is important in photosynthesis, the process by which carbon dioxide is converted into organic substances. The process is a complicated one and still not completely understood, in spite of an enormous amount of research devoted to a solution of the problem. A substance that is known to be formed early in the process of photosynthesis is phosphoglyceric acid. This has been detected by starting with carbon dioxide having radioactive carbon.

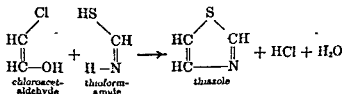
There are two chlorophylls, *viz.*, chlorophyll *a* and chlorophyll *b* The structure of chlorophyll *a* is remarkably like that of heme. It differs in that ring *C* and the vinyl side chain on ring *B* are reduced, the propionic acid side chain of this ring *C* enters into ring formation with an adjacent methine group, the carboxyl groups are esterified with methyl and phytyl alcohols, and it has magnesium in place of the iron of heme. Chlorophyll *b* differs in having an aldehyde group on ring *B*, in place of a methyl group.

Pyrrolidine, C_4H_9N. This can be prepared: (*a*) from pyrrole by reduction with hydriodic acid and phosphorus or with hydrogen and a catalyst (Ni or Pt); (*b*) from succinimide, with sodium and alcohol, the reduction proceeding through the pyrrole stage.

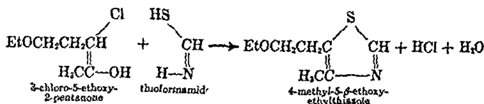


Pyrrolidine is a cyclic secondary amine. It is miscible with water.

Thiazole, C_3H_3NS. This ring system is found in vitamin B_1 (p. 694). Thiazole is formed by a reaction between chloroacetaldehyde and thioformamide. These usually are assumed to react in their enolic forms, because products of more complicated reactions are better accounted for on such a basis.



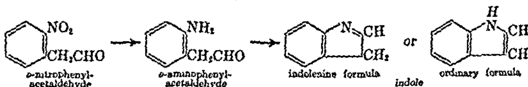
A synthesis important in vitamin B_1 chemistry is the reaction of 3-chloro-5-ethoxy-2-pentanone with thioformamide.



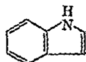
Indole, C_8H_7N, and Related Compounds. Indole was first prepared from oxindole, a degradation product of the blue dye, indigo, by heating it with zinc dust (Baeyer, 1866). The name signifies the mother substance of indigo.

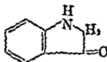
Indole occurs in jasmine flower oil and neroli oil and is a constituent of coal tar. It is formed in the intestinal tract from proteins by the action of certain bacteria on tryptophane (p. 588). It is used in perfumes and for this purpose must be highly purified, because as ordinarily prepared it has a disagreeable odor.

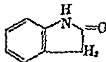
Indole can be synthesized by a closing of the pyrrole ring. One method is the reduction of *o*-nitrophenylacetaldehyde with iron powder and sodium bisulfite solution. The amino compound spontaneously changes to indole.

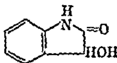


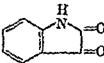
A number of interesting compounds are related to indole.

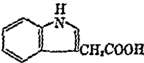

indole


indoxyl

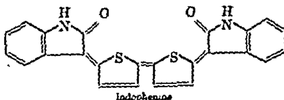

oxindole


dioxindole


isatin


heteroauxin

Indoxyl is important as an intermediate in the synthesis of indigo (p. 717). Indophenine, the substance responsible for the intense blue color obtained in a test for thiophene (p. 665), is formed from two molecules of isatin and two of thiophene.

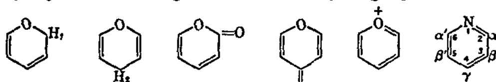

Indophenine

The long conjugated system is responsible for the intense color.

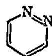
β-Indole-3-acetic Acid, Heteroauxin, $C_{10}H_9O_2$. This is the best-known of the plant growth hormones. It is produced most abundantly in the apical buds and young leaves of plants. It promotes cell elongation and causes numerous changes in plants, such as the induction of new roots.

SOME SIX-MEMBERED HETEROCYCLIC RINGS

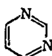
The more important six-membered heterocyclic ring systems are shown below and, in addition, some of the bicyclic compounds having one or more benzene rings fused to a heterocyclic ring. Of the rings shown all are aromatic except those of pyran, pyrone, piperidine, and piperazine. As in the case of the five-membered compounds, only the hetero atoms are shown and an unoccupied position of the ring is a methine or methylene group.



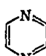
α-pyran (not known) γ-pyran (not known) α-pyrone γ-pyrone pyrylium ion pyridine



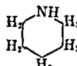
pyridazine 1,2-diazine



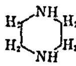
pyrimidine 1,3-diazine



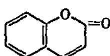
pyrazine 1,4-diazine



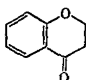
piperidine



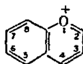
piperazine



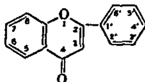
benzo-α-pyrone coumarin



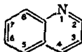
benzo-γ-pyrone chromone



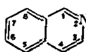
benzopyrylium ion



2-phenyl-5,6-benzo-γ-pyrone flavone

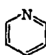


quinoline

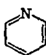


isoquinoline

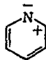
Resonance in Six-Membered Heterocycles. In any monocyclic system, such as pyridine, the main contribution is made by the two Kekulé structures, VIII and IX. In addition, there are contributions by less stable forms, X, XI, and XII.



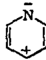
VIII



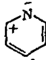
IX



X



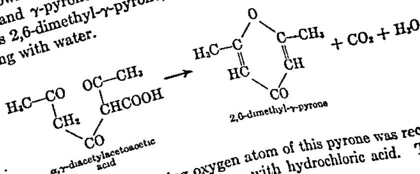
XI



XII

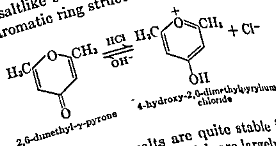
The presence of positive charges at the 2-, 4-, and 6-positions would be expected to lower the reactivity at these positions, an effect which is the opposite of that observed in five-membered heterocycles. Actually, pyridine is much less reactive than benzene towards electrophilic reagents. On the other hand, it is more reactive than benzene towards nucleophilic reagents. The conditions characteristic of the pyridine ring hold also for the pyridazine and other similar aromatic ring systems.

Pyrones. These are either α- or γ-oxopyrans. The pyrans themselves are not known. The pyrone ring is more stable than the pyran ring, for both α-pyrone and γ-pyrone are known. One of the best known of the simple pyrones is 2,6-dimethyl-γ-pyrone, obtained from α,γ-diacetylacetoacetic acid by heating with water.



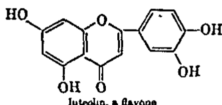
α,γ-diacetylacetoacetic acid; 2,6-dimethyl-γ-pyrone

The basic nature of the ring oxygen atom of this pyrone was recogni[...] the formation of a saltlike substance with hydrochloric acid. This [...] known to have an aromatic ring structure.

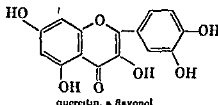


2,6-dimethyl-γ-pyrone; 4-hydroxy-2,6-dimethylpyrylium chloride

This and other similar pyrylium salts are quite stable in water [...] contrast to the oxonium salts of ethers, which are largely hydroly[...] ous solution. The stability of pyrylium salts is ascribed to the [...] of the positive ion, as a result of its aromatic character. The p[...] ture is found in many of the brilliant colors of flowers and fr[...] cyanines.



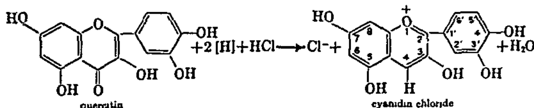
luteolin, a flavone



quercitin, a flavonol

These colors are closely related in structure to those of the anthocyanidins.

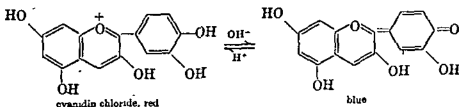
Anthocyanins (Anthocyans) and Anthocyanidins. The most important and most brilliant group of flower and fruit pigments are the anthocyanins. These are glucosides of anthocyanidins, highly colored hydroxy compounds having the carbon skeleton of the flavones and flavonols but differing in having a benzpyrylium nucleus. This relationship is shown by the fact that quercitin, a flavonol, is reduced by zinc and hydrochloric acid to cyanidin chloride, an anthocyanidin. The yield is only 2 per cent.



quercitin cyanidin chloride

The usual method of obtaining an anthocyanin is extraction of the flower or fruit with methanolic hydrogen chloride. Hydrolysis of the anthocyanin with 20 per cent hydrochloric acid gives the corresponding anthocyanidin. There are a number of anthocyanidins. Three of the best known are: pelargonidin chloride, 3,5,7,4′-tetrahydroxy-2-phenylbenzopyrylium chloride, obtainable from the scarlet pelargonium, purple aster, red salvia, and strawberries; cyanidin chloride, 3,5,7,3′,4′-pentahydroxy-2-phenylbenzopyrylium chloride, from a large number of flowers and fruits, especially the red rose, blue cornflower, black cherry, and blackberry; and delphinidin chloride, 3,5,7,3′,4′,5′-hexahydroxy-2-phenylbenzopyrylium chloride, from the blue larkspur, violet pansy, and red vetch. All of the anthocyanidin chlorides are red.

With one equivalent of a strong base the color of these compounds changes from red to violet or blue, and with an excess of base, to a purer blue. A change in structure is involved.



cyanidin chloride, red blue

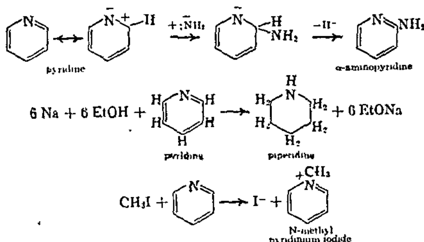
In the naturally occurring anthocyanins, a sugar molecule is always attached to carbon atom C-3 of the anthocyanidin through a glycosidic link.

Sometimes more than one sugar residue is present. The color given by a particular anthocyanidin may vary with the nature or number of sugar residues, or with the pH; thus cyanidin is present (in combination) as a red pigment in the red rose and as a blue pigment in the blue cornflower.

Pyridine, C_5H_5N. This and a number of homologs are present in coal tar. They are removed from different fractions by extraction with sulfuric acid and recovered from the latter by neutralization of the acid with an alkali hydroxide or carbonate, followed by steam distillation. Pyridine and related compounds are also present in bone oil. Pyridine is miscible with water, alcohol, and ether; it has a characteristic, unpleasant odor. As a base it is weaker than ammonia and stronger than pyrrole ($K_b = 2.3 \times 10^{-9}$); it forms salts with aqueous strong acids. Pyridine and pyridine derivatives can be synthesized by a number of ring closure reactions. Many require a high temperature. Pyridine, for example, is formed when ammonia, formaldehyde, and acetaldehyde are passed as vapor over hot aluminum oxide.

The outstanding characteristic of pyridine is its chemical inertness. It resists the action of such oxidizing agents as chromic acid, potassium permanganate, and nitric acid. It undergoes substitution with difficulty, with formation of β-substitution products (p. 672). Sulfonation with sulfuric acid (100% acid for three days), nitration with potassium nitrate in fuming sulfuric acid, and bromination with bromine all require temperatures of about 300°. It does not undergo the Friedel-Crafts type of reaction.

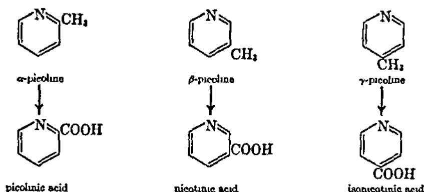
The main reactions that pyridine undergoes readily are amination, reduction, and alkylation at the nitrogen atom. The first takes place with sodamide, the second with hydrogen (catalytically) or with sodium in absolute alcohol, and the third with an alkylating agent.



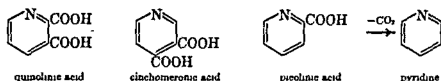
The reduction of pyridine to piperidine establishes the structure of pyridine. More vigorous reduction causes opening of the ring: for example, hydrogen with a nickel catalyst at 180° gives *n*-amyl amine, and at 220°, *n*-pentane and ammonia, a result given also by heating with hydriodic acid at 300° under pressure.

Heating a methyl or ethylpyridinium halide to about 300° results in a migration of the alkyl group to the 2- or 4-position on the ring. Isomerizatiôn of the alkyl radical may take place with *n*-propyl or higher radical. The former gives some isopropyl derivative.

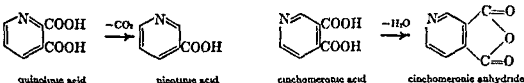
Picolines, C_6H_7N. These are methylpyridines. Oxidation converts them to acids.



Pyridine Carboxylic Acids. These often are obtained by the oxidation of alkaloids. Their formation indicates the presence of either pyridine or piperidine rings in the alkaloids from which they are obtained. Other important acids in addition to those just mentioned are quinolinic and cinchomeric acids.



Nicotinic acid results from the oxidation of the alkaloid nicotine, quinolinic acid from quinoline, and cinchomeronic acid from the alkaloid cinchonine. All these acids when heated with lime are converted into pyridine by loss of carbon dioxide. When the carboxyl group is in the α-position, strong heating alone will bring about this change, for picolinic acid is converted into pyridine and quinolinic acid into nicotinic acid.

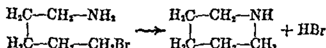


Cinchomeronic acid can be converted into an anhydride by heating with acetic anhydride. Since quinolinic and cinchomeronic acids yield anhydrides by this treatment, the carboxyl groups must be adjacent to each other.

Piperidine, $C_5H_{11}N$. This was first obtained by the hydrolysis of piperine, one of the alkaloids of pepper. It is a colorless liquid, miscible with water, alcohol, and ether. As a base it is much stronger than pyridine. Its constant is that of a secondary amine, $K_b = 1.6 \times 10^{-3}$. It forms salts with acids and precipitates heavy metal hydroxides. Piperidine has the proper

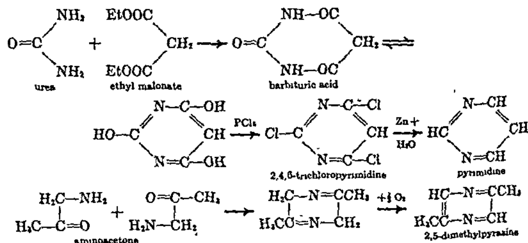
ties of an antioxidant and is useful with synthetic rubber. It is a good catalyst for a number of reactions, for example, the condensation of aldehydes with malonic acid (p. 192).

Piperidine can be obtained from pyridine by reduction (p. 674). It can be synthesized by ring closure of a number of derivatives of 1-aminopentane, for example, 1-amino-5-bromopentane, 5-amino-1-pentanol, and 1,5-diaminopentane. Addition of base to a salt of 1-amino-5-bromopentane results in the formation of piperidine, and heating the dihydrochloride of the diamine results in the elimination of ammonium chloride and the formation of the hydrochloride of piperidine (p. 364).



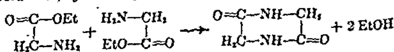
Also, piperidine is formed from 1,5-dibromopentane and ammonia in ether solution. These various syntheses establish the structure of piperidine, and thus of pyridine, since it is easily reduced to piperidine.

Diazines, $C_4H_4N_2$. These are pyridazine, pyrimidine, and pyrazine (p. 671). They and numerous derivatives can be prepared by a variety of ring closure methods. As examples, pyrimidine may be obtained from urea and ethyl malonate, and disubstituted pyrazines from α-amino ketones.



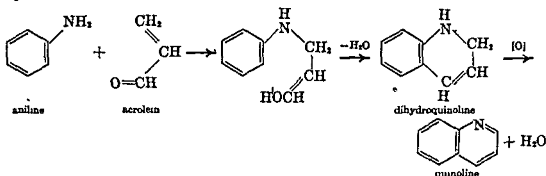
Quite a number of natural products have a diazine ring system; for example, uric acid, vitamin B, folic acid, theobromine, adenine, and xanthine have a pyrimidine ring system, and folic acid has also a pyrazine ring (p. 696).

Piperazine, $C_4H_{10}N_2$. This is formed by heating the hydrochloride of ethylene diamine (p. 364) or by reduction of pyrazine with sodium and alcohol. Its basic constant, $K_b = 6.4 \times 10^{-5}$, is a little less than that of a primary aliphatic amine. The most important derivatives of piperazine are the diketopiperazines, cyclic anhydrides of α-amino acids (p. 584)



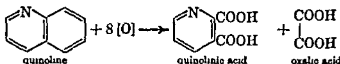
Quinoline, C_9H_7N. This is present in the decomposition products of the alkaloid, quinine, when the latter is heated. The name signifies a relationship between the two. Quinoline is present in coal tar and in bone oil. It has a characteristic, unpleasant odor but not nearly so disagreeable as pyridine. It is a weak base, comparable in strength to pyridine ($K_b = 3.2 \times 10^{-10}$).

The most convenient preparation of quinoline is by the Skraup synthesis, in which a mixture of aniline, nitrobenzene, glycerol, and sulfuric acid is heated. The reaction is believed to proceed in steps. Acrolein is formed from glycerol by the action of sulfuric acid. The reaction of acrolein with aniline is believed to proceed by a 1,4-addition, because such a mechanism accounts for the products formed with crotonaldehyde and other higher aldehydes.



Nitrobenzene acts as an oxidizing agent to oxidize the dihydroquinoline to quinoline, and in so doing is reduced to aniline. Other mild oxidizing agents can replace nitrobenzene, for example, arsenic acid.

The structure of quinoline is established by a number of reactions, of which its behavior on oxidation is important. Potassium permanganate yields quinolinic acid and oxalic acid.



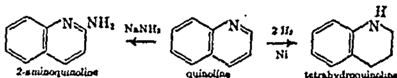
Quinoline thus has a pyridine ring in addition to the benzene ring, as indicated by its synthesis.

Electrophilic reagents usually attack the benzene ring, because the pyridine ring is unreactive. Fuming sulfuric acid at 180° yields quinoline-5-sulfonic and quinoline-8-sulfonic acids; concentrated sulfuric acid and quinoline nitrate yield 5-nitro- and 8-nitroquinoline at ordinary temperature; but bromine attacks the pyridine ring, giving 3-bromoquinoline at 200° in the presence of sulfur.

Vigorous oxidation usually oxidizes away the benzene ring with formation of quinolinic acid, as with alkaline permanganate. This takes place even when a nitro group is attached to the benzene ring.

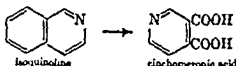
Nucleophilic reagents attack the pyridine ring. With sodamide, 2-aminoquinoline is formed. Reducing agents, for example, sodium and alcohol, zinc

and hydrochloric acid, or controlled hydrogenation at 160° give *tetrahydroquinoline*.



Decahydroquinoline can be obtained by continued hydrogenation.

Isoquinoline, C_9H_7N. This is present in coal tar. Oxidation to cinchomeronic acid (p. 675) establishes its structure.



Isoquinoline has a basic strength ($K_b = 1.1 \times 10^{-9}$) comparable to those of pyridine and quinoline. Many alkaloids, among them morphine, have an isoquinoline nucleus.

PROBLEMS

1. Show how to synthesize the following from acyclic compounds:

a) 3,5-dimethyl-2-ethylpyrrole
b) 3,5-dimethyl-2-*n*-propylpyrrole
c) 2,3,4-trimethyl-5-ethylpyrrole
d) 5-methyl-2,3-diethylpyrrole
e) 2,3,4-trimethylpyrrole
f) 2-methyl-3,4-diethylpyrrole

2. Ditto, but starting with nonnitrogenous acyclic compounds.

3. Show how to synthesize the following, starting with ethyl acetoacetate:

a) 2,5-dimethylfuran
b) 2,3,5-trimethylthiophene
c) 2-methyl-5-ethylpyrrole
d) 2,3,5-trimethylfuran
e) 2,5-dimethyl-3-ethylthiophene
f) 2,5-dimethyl-3,4-dicarbethoxypyrrole
g) 3,5-dimethyl-2-ethylfuran
h) 3,5-dimethyl-2-*n*-propylthiophene
i) 3,4-dimethylpyrrole
j) 2-ethyl-3,4-dimethylpyrrole

4. Show how to obtain the following from a monocyclic compound:

a) 3-aminopyridine
b) 2-ethylquinoline
c) 8-methylquinoline
d) 2,6-dimethylquinoline
e) 8-ethylquinoline
f) 6-chloroquinoline
g) 8-hydroxyquinoline
h) 8-chloro-2-methylquinoline
i) pyridine-2,3-dicarboxylic acid
j) pyridine-2,3,6-tricarboxylic acid
k) 2-aminoquinoline
l) nicotinic acid

5. Show how the following pairs of compounds may be separated so as to recover one component essentially quantitatively.

a) thiophene and benzene
b) benzene and pyridine
c) toluene and piperidine
d) β-methylnaphthalene and quinoline
e) β-naphthol and isoquinoline
f) pyrimidine and *m*-xylene

6. Show the possible number of resonance forms of the following in which octets are complete. In *g*, *h*, *i*, and *j* retain a complete system of alternate single and double bonds around the molecule.

a) coumarin
b) chromone
c) quinoline
d) isoquinoline
e) flavone
f) cyanidin chloride
g) protoporphyrin
h) heme
i) chlorophyll *a*
j) chlorophyll *b*

CHAPTER 45

Alkaloids and Drugs

The term alkaloid is now generally understood to mean
compound of plant origin (or rarely, of animal origin, as a
name alkaloid means alkalilike, and was given in 1806 by
coverer of the first alkaloid, morphine, to denote its basic
loids embrace both liquids and solids (mainly solids) and
soluble in water, soluble in dilute aqueous hydrohalic
in plants they are in the form of salts, in combination with
acetic, oxalic, lactic, malic, tartaric, citric, fumaric, tigli
method of isolation generally applicable is extraction of
hydrochloric acid. Enough base is added to neutralize the
Often the alkaloid separates out at this point. It is
solvent, the aqueous phase is extracted, and on
solid, crystallizes. Purification is accomplished by
the most commonly used solvents for extraction is chloroform,
all alkaloids are readily soluble in it.

Alkaloids are noted for possessing pronounced
The medicinal value of numerous plants or plant extracts have
since ancient times. In a great many cases the active principle is
Some alkaloids are soporifics, for example, morphine; some a
thetics, for example, cocaine; some are very poisonous, for
nine and nicotine. Almost all are poisonous to some extent,
account there usually is danger in taking any alkaloid for a
An overdose may be fatal.

It is the aim of this chapter to show how the structures of
simpler alkaloids have been determined, and to give the structu
other, more complicated alkaloids. In addition, mention will
some synthetic drugs and of vitamins having heterocyclic rings

The natural bases classified as alkaloids are cyclic comp
physiologically potent aliphatic bases are usually included
compounds, rather than with the alkaloids. The ring syste
with the exception of a relatively small number derived fr
heterocyclic. Such ring systems may be: pyrrole, imidazole

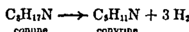
idine, quinoline, isoquinoline, or the corresponding reduced rings. Benzene rings may also be present. Alkaloids usually are classified largely on the basis of the ring systems. Only a limited number of the simpler alkaloids are considered here.

Functional groups that may be present in the alkaloid molecule are —OH(alcoholic and phenolic hydroxyl), —OMe(methoxyl), $=O_2CH_2$(methylenedioxy), $—NH_2$(amino), —NHMe(methylamino), $—NMe_2$(dimethylamino), —COOH(carboxyl), —COOR(carbalkoxyl), and —CONHR(carbamido); less common, —CO—(carbonyl), $—CH=CH_2$(vinyl), and —C≡N(nitrile).

Methods of Structure Determination. The most important fact to establish is the nature of the heterocyclic system, then the nature of the functional groups, and then the position of these. In addition, the stereochemical arrangement must be established in the case of optically active alkaloids.

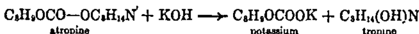
The fundamental ring system sometimes becomes evident at elevated temperatures under conditions that promote decarboxylation, dehydrogenation, or mild oxidation. Functional groups can be detected by general reactions and usually can be determined quantitatively by standard methods. Reduced rings can be opened by degradative methods.

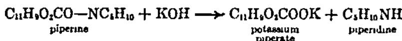
1. *Distillation of hydrohalic salts with zinc dust.* This reduces the phenolic function to hydrogen and brings about the dehydrogenation of reduced rings.



2. *Alkali fusion.* This often causes dehydrogenation of oxidizable side chains and decarboxylation of aromatic acids (p. 504). Thus, cinchonine yields 4-methylquinoline, and quinine yields 6-methoxy-4-methylquinoline.

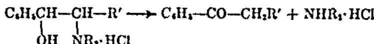
3. *Hydrolysis.* This cleaves ester and amide linkages; these are respectively present in the molecule of the alkaloids atropine and piperine.





4. *Cleavage with hydriodic acid (Zeisel).* Methoxyl groups (less readily, methylamino groups) yield methyl iodide, which can be determined quantitatively with standard silver nitrate.

5. *Hydramine fission.* If a side chain attached to a benzene ring has a hydroxyl group at the α-position and an amino or substituted amino group at the β-position, heating the hydrochloride of the compound results in the formation of ammonium (or alkylammonium) chloride and an α-ketone.



CHAPTER 45

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The term alkaloid is now generally understood to mean a nitrogenous basic compound of plant origin (or rarely, of animal origin, as adrenalin). The name alkaloid means alkalilike, and was given in 1806 by Serturner, the discoverer of the first alkaloid, morphine, to denote its basic character. Alkaloids embrace both liquids and solids (mainly solids) and usually they are insoluble in water, soluble in dilute aqueous hydrohalic acids. As they occur in plants they are in the form of salts, in combination with acids, among them acetic, oxalic, lactic, malic, tartaric, citric, fumaric, tiglic, and quinic. A method of isolation generally applicable is extraction of the plant with dilute hydrochloric acid. Enough base is added to neutralize the hydrochloric acid. Often the alkaloid separates out at this point. It is dissolved in a suitable solvent, the aqueous phase is extracted, and on evaporation the alkaloid, if solid, crystallizes. Purification is accomplished by recrystallization. One of the most commonly used solvents for extraction is chloroform, because almost all alkaloids are readily soluble in it.

Alkaloids are noted for possessing pronounced physiological properties. The medicinal value of numerous plants or plant extracts have been known since ancient times. In a great many cases the active principle is an alkaloid. Some alkaloids are soporifics, for example, morphine; some are local anesthetics, for example, cocaine; some are very poisonous, for example, strychnine and nicotine. Almost all are poisonous to some extent, and on that account there usually is danger in taking any alkaloid for a specific purpose. An overdose may be fatal.

It is the aim of this chapter to show how the structures of some of the simpler alkaloids have been determined, and to give the structures of some other, more complicated alkaloids. In addition, mention will be made of some synthetic drugs and of vitamins having heterocyclic rings.

The natural bases classified as alkaloids are cyclic compounds. Many physiologically potent aliphatic bases are usually included with aliphatic compounds, rather than with the alkaloids. The ring systems of alkaloids, with the exception of a relatively small number derived from benzene, are heterocyclic. Such ring systems may be: pyrrole, imidazole, pyridine, pyrim-

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Methods of Structure Determination. The most important fact to establish is the nature of the heterocyclic system, then the nature of the functional groups, and then the position of these. In addition, the stereochemical arrangement must be established in the case of optically active alkaloids.

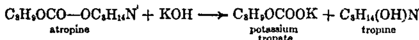
The fundamental ring system sometimes becomes evident at elevated temperatures under conditions that promote decarboxylation, dehydrogenation, or mild oxidation. Functional groups can be detected by general reactions and usually can be determined quantitatively by standard methods. Reduced rings can be opened by degradative methods.

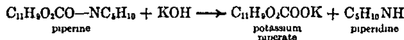
1. *Distillation of hydrohalic salts with zinc dust.* This reduces the phenolic function to hydrogen and brings about the dehydrogenation of reduced rings.



2. *Alkali fusion.* This often causes dehydrogenation of oxidizable side chains and decarboxylation of aromatic acids (p. 504). Thus, cinchonine yields 4-methylquinoline, and quinine yields 6-methoxy-4-methylquinoline.

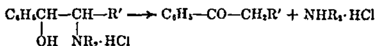
3. *Hydrolysis.* This cleaves ester and amide linkages; these are respectively present in the molecule of the alkaloids atropine and piperine.





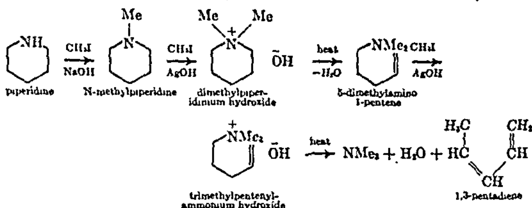
4. *Cleavage with hydriodic acid (Zeisel).* Methoxyl groups (less readily, methylamino groups) yield methyl iodide, which can be determined quantitatively with standard silver nitrate.

5. *Hydramine fission.* If a side chain attached to a benzene ring has a hydroxyl group at the α-position and an amino or substituted amino group at the β-position, heating the hydrochloride of the compound results in the formation of ammonium (or alkylammonium) chloride and an α-ketone.



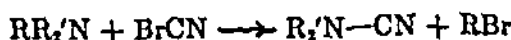
6. *Reduction of aromatic rings.* Hydrogenation (with platinum catalyst) or heating with metallic sodium and alcohol usually causes reduction of aromatic rings (p. 674).

7. *Opening reduced rings.* There are a number of methods. Heating with hydriodic acid and phosphorus to 300° reduces pyrrolidine (p. 669) to *n*-pentane; preferred to this are methods that are more gradual, and yield products that still have functional groups, for example, the Hofmann degradation of quaternary ammonium bases (p. 374), the cyanogen bromide method of von Braun, and the opening of the ring of a benzoylated derivative. The opening of the piperidine ring by these methods is outlined below.



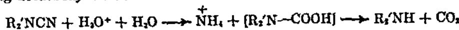
In the Hofmann degradation the quaternary base, dimethylpiperidinium hydroxide, when heated decomposes, by scission of a C—N bond and production of a C=C double bond. The product, 5-dimethylamino-1-pentene, is then converted to a second quaternary base. When this is heated the second C—N bond is cleaved, with formation of trimethylamine and 1,3-pentadiene. The expected product, 1,4-pentadiene, rearranges under the conditions of the experiment, to give the more stable isomer.

Cyanogen bromide reacts readily with most tertiary amines. The initial quaternary ammonium compound is unstable and decomposes into an alkyl bromide and a cyanoamine.



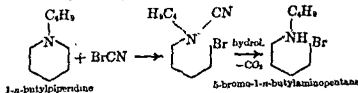
$$RR_2'N + BrCN \longrightarrow R_2'N{-}CN + RBr$$

With different radicals the ease of removal as RBr is in the order: benzyl > allyl > small alkyl > large alkyl. When the cyanoamine is hydrolyzed, it is converted to a secondary amine, the intermediate carboxylic acid undergoing decarboxylation.

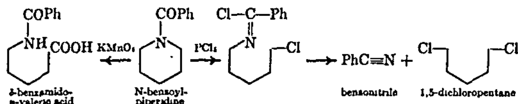


$$R_2'NCN + H_3O^+ + H_2O \longrightarrow \overset{+}{N}H_4 + [R_2'N{-}COOH] \longrightarrow R_2'NH + CO_2$$

When the nitrogen atom is part of a reduced ring system, the ring usually opens if R is not benzyl or allyl; good results are obtained if it is *n*-butyl.



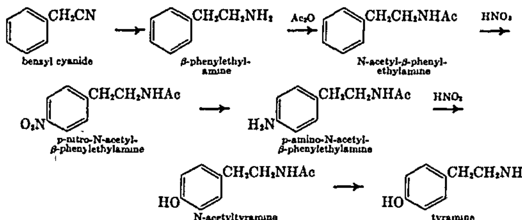
Benzoylpiperidine undergoes ring opening when oxidized with permanganate, or by the action of phosphorus pentachloride.



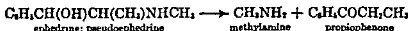
DERIVATIVES OF β-PHENYLETHYLAMINE

There are a number of physiologically potent nitrogeneous bases having carbocyclic ring systems. These are derivatives of benzene, in particular, β-phenylethylamine. Many are of animal origin.

Tyramine, β-p-Hydroxyphenylethylamine, p-$HOC_6H_4CH_2CH_2NH_2$, m.p. 164°. This is one of the active principles of ergot. When injected it causes a marked rise in blood pressure. It is believed to be formed by decarboxylation of the amino acid, tyrosine. This has been observed to take place with some bacteria, and also when heated in a high boiling solvent, for example, diphenylamine. Tyramine can be synthesized from benzyl cyanide by standard reactions.

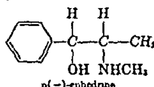


Ephedrine, m.p. 73–74°, $[\alpha]_D - 6°$, and Pseudoephedrine, m.p. 118–119°, $[\alpha]_D + 50°$, $C_6H_5CH(OH)CH(NHCH_3)CH_3$. These isomeric bases are present in the Chinese plant, mahuang (*Ephedra sinica*), used for centuries as a medicine and drug by the Chinese. Oxidation of ephedrine or pseudoephedrine yields benzoic acid. This shows the presence of a benzene ring having only one side chain and no amino or hydroxyl group attached to the benzene ring. The formation of a dibenzoyl derivative with benzoyl chloride shows the presence of the hydroxyl and an amino or secondary amino group. On heating the hydrochloride, hydramine fission yields methylammonium chloride and ethyl phenyl ketone. This shows that the side chain is n-propyl, with the hydroxyl group at the α-position and the methylamino group at the β-position.

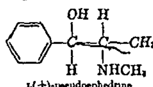


There are two asymmetric carbon atoms in the molecule, and thus there are four stereoisomers, two pairs of antipodes. Ephedrine, the most important of the bases present in the plant, is levorotatory; pseudoephedrine, dextrorotatory. Ephedrine can be administered orally. It exerts a pressor action (increases blood pressure) by causing the arterioles to contract and a mydriadic action (dilation of the pupil of the eye), and it dilates the bronchi. It is useful in the treatment of asthma, hay fever, and allergies. Pseudoephedrine has similar but milder effects. Many other remedies used for these purposes, benzedrine, for example, are related structurally to β-phenylethylamine.

The configuration of ephedrine has been established by relating the configuration of the α-carbon atom (the one holding the hydroxyl group) to D(−)-mandelic acid and that of the β-carbon atom to L(+)-alanine. The assignment to the D- or L-family is made on the basis that numbering starts at the methyl group and the family is determined by the highest numbered asymmetric carbon atom. Ephedrine has the *erythro-* and pseudoephedrine has the *threo*-configuration. These terms refer to the configurations of the two tetroses, erythrose and threose (p. 627), and to the relative positions of the substituent groups (in these cases, one hydroxyl group and one methylamino group) that are attached to the two asymmetric carbon atoms.

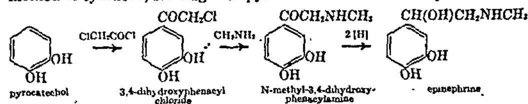


D(−)-ephedrine



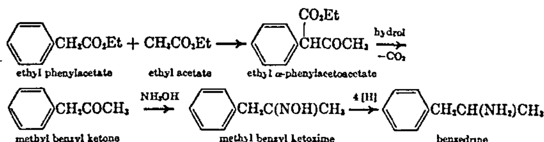
L(+)-pseudoephedrine

Epinephrine, Adrenalin, 1-(3,4-Dihydroxyphenyl)-2-methylamino-1-ethanol, m.p. 206–212°, $[\alpha]_D - 51°$. This is the active principle of the suprarenal gland. It is a hormone, much simpler in structure than many that have a protein structure (p. 606), and the first to be isolated. The adrenal gland secretes this hormone directly into the blood stream, with resultant increase in blood pressure. The same effect is observed if the drug is injected. It is inactive when administered orally. The structure is indicated by the method of synthesis, starting with pyrocatechol and chloroacetyl chloride.

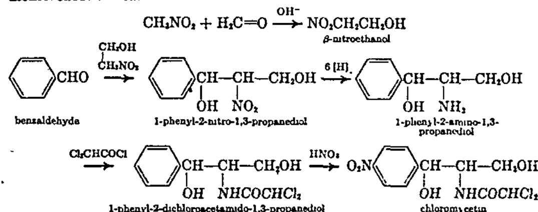


The synthetic product is optically inactive, and is resolved into active forms with tartaric acid. The natural product is L(−)-epinephrine. This has a pressor activity about twice that of the synthetic product, and about twenty times that of the (+)-isomer.

Benzedrine, $C_6H_5CH_2CH(NH_2)CH_3$. This is a synthetic drug much used for asthma and allergies. One method of synthesis starts with a Claisen condensation between ethyl acetate and ethyl phenylacetate.



Chloromycetin, Chloramphenicol, D(−)-*threo*-1-*p*-Nitrophenyl-2-dichloroacetamido-1,3-propanediol, $C_{11}H_{12}O_5N_2Cl_2$. This is an important antibiotic (p. 691), obtainable from a species of *Streptomyces*. It is one of the simpler antibiotics and the first to be synthesized on a commercial scale (1949). From a structural point of view it is unique among natural products in having a nitro group and a dichloroacetyl group in its structure. It has been synthesized from benzaldehyde, nitromethane, formaldehyde, and dichloroacetic acid.



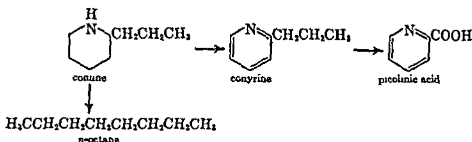
Since there are two asymmetric carbon atoms in the molecule of chloromycetin, there are four optically active forms, as in the case of the ephedrines; the naturally occurring form has the D-*threo*-configuration (p. 684). It has been found to be of value in the treatment of a number of ailments, for example, typhus, typhoid fever, and whooping cough.

DERIVATIVES OF PYRIDINE AND PIPERIDINE

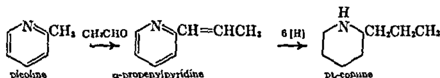
Coniine, $C_8H_{17}N$, m.p. −20°, b.p. 168°, $[\alpha]_D + 15.7°$. This is found in the poison hemlock, *Conium maculatum*, a shrub growing in wet locations. The alkaloid is concentrated in the seeds, although it is distributed throughout the plant. Coniine is one of the simpler alkaloids. It is interesting historically not only because it was the poison that Socrates and others condemned to die were required by the Greeks to drink, but also because it was the first alkaloid to be synthesized (Ladenburg, 1886).

The structure of coniine has been established by means of relatively simple reactions (A. W. Hofmann; A. Ladenburg): (1) distillation of the hydrochloride with zinc dust, which causes dehydrogenation of coniine to con-

$C_8H_{11}N$; (2) heating conyrine with a strong oxidizing agent to give picolinic acid; (3) heating coniine with hydriodic acid and phosphorus to 300°, which yields *n*-octane; (4) exhaustive methylation of coniine, which yields a normal octadiene, conylene. The first reaction indicates the conversion of the reduced ring of coniine to the aromatic ring of conyrine, by loss of hydrogen. The second reaction shows that conyrine has a pyridine ring and a side chain in the α-position. The third and fourth reactions are ring openings and prove that the side chain is normal. These changes show that coniine is α-*n*-propylpiperidine.

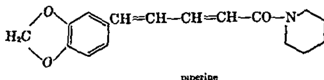


Coniine was synthesized by Ladenburg from picoline. This reacts with aldehyde to form α-propenylpyridine, which on reduction with sodium and alcohol is converted to DL-coniine.



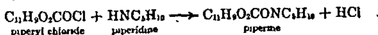
Resolution of DL-coniine with tartaric acid gave (+)-coniine, identical with the natural product.

Piperine and Chavicine, $C_{17}H_{19}O_3N$. These are isomeric alkaloids found in pepper (*Piper nigrum*, *Piper longum*), and are responsible for the peppery taste. Piperine, m.p. 129.5°, is the more abundant alkaloid (5–9%) but chavicine is more potent. On hydrolysis with base, piperine is converted to piperidine and a salt of piperic acid, $CH_2O_2C_6H_3CH{=}CH{-}CH{=}CHCOOH$. Piperine thus has an amide structure.



piperine

It has been synthesized by the reaction of piperyl chloride and piperidine.



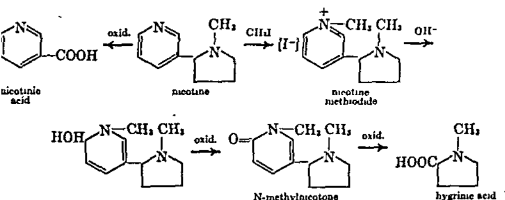
Piperine is the *trans,trans*-isomer, and chavicine is the *cis,cis*-isomer.

Nicotine, $C_{10}H_{14}N_2$, b.p. 246°, $[\alpha]_D$ −169°. This is the chief alkaloid of the tobacco plant (*Nicotiana tabacum*), where it is present as a salt of malic

or citric acid. Although it is distributed throughout the plant, its highest concentration is found in the leaves, in varying amounts (0.6–8%). Nicotine when pure is a colorless liquid, miscible with water between 60° and 210° and possesses an unpleasant odor. It darkens on exposure to air. It is one of the most poisonous of all drugs. The lethal dose is 30 to 50 mg.

Nicotine reacts with methyl iodide to form a dimethiodide and two monomethiodides but does not form a benzoyl or acetyl derivative. Thus the two nitrogen atoms of nicotine are tertiary. Oxidation of nicotine with chromic acid or permanganate yields nicotinic acid. This indicates the presence of a pyridine ring with some sort of group attached at the β-position, which is shown below to be a pyrrolidine ring.

The pyridine ring is opened by converting nicotine to a methiodide, adding alkali to obtain the pseudo base, oxidizing this with a mild oxidizing agent (potassium ferricyanide) to a ketone, nicotone, and then oxidizing this to hygrinic acid (N-methylpyrrolidine-α-carboxylic acid), with destruction of the original pyridine ring.



Nicotine is thus shown to have both a pyrrolidine and a pyridine nucleus in its structure. It is 1-methyl-2-β-pyridylpyrrolidine.

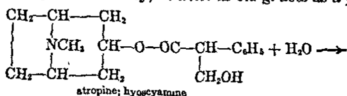
ALKALOIDS WITH CONDENSED PYRROLIDINE AND PIPERIDINE RINGS

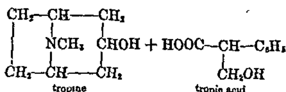
The two most important alkaloids of this type are atropine and cocaine. Their structures are too complicated to be elucidated here.

Atropine, m.p. 118°, and Hyoscyamine, m.p. 108.5°, $C_{17}H_{23}O_3N$. These occur together in the stems of belladona, the deadly nightshade (*Atropa belladona*), and in related plants. Hyoscyamine is levorotatory, $[\alpha]_D - 24°$, and on standing slowly racemizes to atropine. These are esters of the bicyclic hydroxy tertiary amine, tropine, and the hydroxy acid, tropic acid. Tropic acid from hyoscyamine by hydrolysis with water is also levorotatory, but when obtained by acidic or basic hydrolysis is inactive.

The main use of atropine in medicine is related to its powerful mydriatic action. It may be administered either externally or internally. Externally

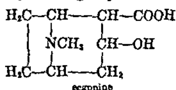
one part in 130,000 parts of water exerts a noticeable effect on the pupil of the eye. Internally, as little as 0.1 g. acts as a poison.

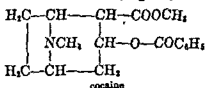




Cocaine, $C_{17}H_{21}O_4N$, m.p. 98°, $[\alpha]_D$ −15.8°. This is present in the leaves of the coca plant (*Erythroxylon coca*), a tropical shrubby plant, not to be confused with cacao (cocoa), the source of chocolate and cocoa. South American coca leaves contain 1.6 per cent of alkaloids of which about 65 per cent is cocaine. It is used as a local anesthetic.

On hydrolysis cocaine yields methanol, benzoic acid, and ecgonine, a tertiary base very similar to tropine except that it has a carboxyl group. Ecgonine therefore is a base, an alcohol, and an acid; and cocaine is the benzoate at the hydroxyl group and the methyl ester at the carboxyl group.

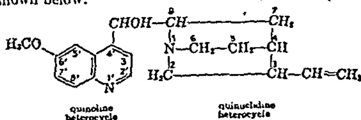




DERIVATIVES OF QUINOLINE

Quinine, $C_{20}H_{24}O_2N_2$, m.p. 177°, $[\alpha]_D$ −158°, and Cinchonine, m.p. 255°, $[\alpha]_D$ + 234°, $C_{19}H_{22}ON_2$. These are the two most important of a number of alkaloids that occur in the bark of the cinchona tree (*Cinchona*), originally found only in South America, but now grown in other tropical countries. At the present time Java is the main producing country and has an essentially complete monopoly in the production of the drug. These alkaloids are antipyretics and are used in the treatment of fever. Quinine also acts as a poison to the microorganisms that cause malaria and is one of the best drugs for control of this disease.

Structurally quinine has two heterocyclic units, *viz.*, quinoline and quinuclidine, attached through a hydroxymethylene group. The formula as usually written is shown below.

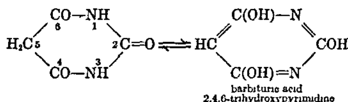


Cinchonine has a similar structure except that it lacks the methoxyl group in the 6′-position.

PYRIMIDINE COMPOUNDS

Among these are the synthetic barbituric acids and many naturally occurring compounds. Examples of the latter are: cystosine, thymine, and uracil, from nucleic acids; the vitamins, thiamine chloride and folic acid; and a number of purine derivatives.

Barbituric Acid, $C_4H_4O_3N_2$. This is formed by a reaction of urea with ethyl malonate (p. 676). Barbituric acid is tautomeric, and in one form is



barbituric acid
2,4,6-trihydroxypyrimidine

a derivative of pyrimidine. The stability of the triketo (lactam) form over the trihydroxy (lactim; enol) form is counterbalanced by the stabilization of the latter arising from its aromatic character, in a manner recalling the tautomerism of phloroglucinol (p. 504). Barbituric acid is a much stronger acid than phloroglucinol ($K_a = 1 \times 10^{-4}$ against 3.7×10^{-8}). This greater acidic character is explained on the basis of the positive charges that resonance places on the 2,4,6-carbon atoms, as in the case of pyridine (p. 671).

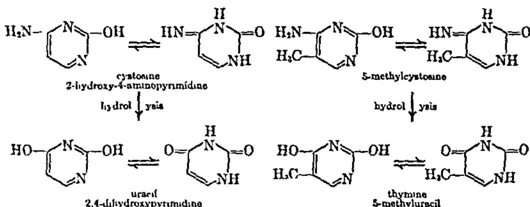
Many derivatives of barbituric acid have a hypnotic and sedative effect when taken internally. In these there are two organic radicals (usually alkyl) attached at the C-5 carbon atom. Owing to the low solubility of the barbituric acids, they are administered as sodium, calcium, or magnesium salts. They are commonly called barbiturates. Two well-known drugs of this type are barbital (veronal), 5,5-diethylbarbituric acid, and phenobarbital, 5-ethyl-5-phenylbarbituric acid. They are made by condensing urea with ethyl diethylmalonate and ethyl ethylphenylmalonate, respectively.

Nucleic Acids. These acids are important constituents of living cells; they may occur free, as in yeast, or in combination with protein as nucleoproteins, as in the thymus gland. Mild hydrolysis of a nucleoprotein, for example, enzymatic hydrolysis, yields the nucleic acid and the protein. There [illegible] ent in all living cells, deoxyribonucleoprotein mainly in the nucleus of the cell, ribonucleoprotein mainly in the cytoplasm of the cell.

The products obtained by acid hydrolysis of ribonucleic acid, in addition to D-ribose, are phosphoric acid, the pyrimidine bases, cystosine and uracil, m.p. 335°, and the purine bases, adenine and guanine (p. 691). Deoxyribonucleic acid yields, in addition to D-deoxyribose, phosphoric acid, the pyrimidine bases, cystosine and thymine, m.p. 326°, and the purine bases, adenine

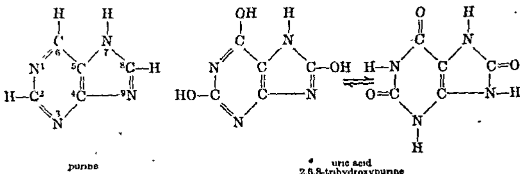
and guanine. The molecular ratios are approximately: sugar, 4, phosphoric acid, 4, and bases, 4. The last are not present in equimolar amounts. The pentose units are attached to each other through phosphate residues by ester linkages, and each pentose unit holds a pyrimidine or purine base by a glycosidic linkage. Molecular weight values for nucleic acids have been found to be as high as three million.

The pyrimidine bases, cytosine and methylcytosine, under vigorous hydrolysis are converted to uracil and thymine, respectively. The four compounds exist in tautomeric forms, as enol and keto forms. The enol forms have the aromatic structure of pyrimidine shown on page 671.



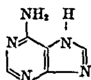
PURINES

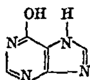
Many important plant and animal compounds are derivatives of purine, m.p. 216–217°, which, however, does not occur naturally. The heterocyclic system of purine is composed of a pyrimidine ring fused with an imidazole ring.

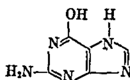


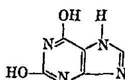
Uric Acid, 2,6,8-Trihydroxypurine. Only traces of uric acid occur in the blood of man and mammals under normal conditions. It is excreted in small quantities in the urine. It is a white, crystalline solid, sparingly soluble in water (0.00645 g. per 100 ml. H_2O). It forms a sparingly soluble monosodium, and a soluble disodium salt (primary and secondary urate, respectively). It does not form salts with aqueous acids.

Urinary calculi and gall stones are largely uric acid; ammonium urate (primary) is also present in both, and sodium urate (primary) is present in calculi. Uric acid is the end product resulting from nitrogen metabolism in birds and reptiles. The excrement of these animals is largely ammonium urate.

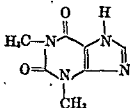

adenine
6-aminopurine

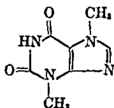

hypoxanthine
6-hydroxypurine

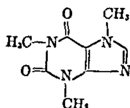

guanine
2-amino-6-hydroxy-purine


xanthine
2,6-dihydroxy-purine

Adenine and guanine have been isolated from nucleic acids. They are thus widely distributed as components of all living cells. Adenine is found also in the free state in animals (muscle, organs), bacteria, many plants (hops, tea, sugar beet), and in yeast. Guanine often accompanies adenine. It occurs also in the scales and skin of fish and reptiles. The characteristic shiny appearance of these is due to the presence of crystallized guanine. Xanthine accompanies caffeine in tea and occurs in other plants. Hypoxanthine occurs widely in plants and animals.


theophylline
1,3-dimethylxanthine


theobromine
3,7-dimethylxanthine


caffeine
1,3,7-trimethylxanthine

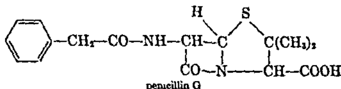
Theophylline (m.p. *ca.* 272°) is present in small quantities in tea leaves. Theobromine (m.p. *ca.* 351°) is present to the extent of 1 to 3 per cent in the cocoa bean, of which it is the principal alkaloid. Caffeine (m.p. *ca.* 236°) is present in the leaves of tea and coffee to the extent of 1 to 4 per cent, in the coffee bean and in the leaves of some other plants, including maté. These three alkaloids exert a stimulating effect on the central nervous system; also, they are diuretics.

ANTIBIOTICS AND SULFA DRUGS

Antibiotics. These are substances produced by living organisms, usually microorganisms such as molds or bacteria. They have the property of interfering with the metabolic processes of other organisms to such an extent that the growth of the second organism is retarded or completely suppressed. Penicillin was the first antibiotic investigated. The antibiotic effect of the green mold, *Penicillium notatum*, was discovered by Alexander Fleming in 1929, and its production was stimulated by the advent of World War II. Penicillin is effective against many diseases produced by streptococci and staphylococci, and is remarkably nontoxic. Penicillin as isolated is a mixture

of a number of closely related compounds. One of the most effective of these is penicillin G.

The characteristic structure of the penicillins is a heterocyclic nucleus consisting of a β-lactam ring fused with a tetrahydrothiazole ring.

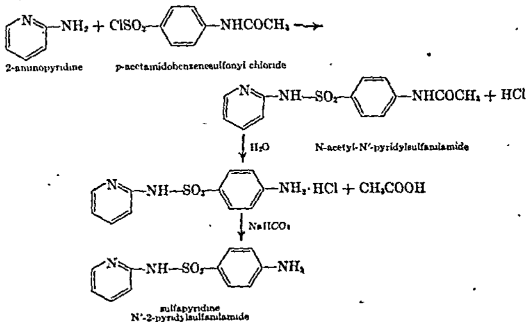


penicillin G

In a number of other penicillins the benzyl group of the side chain is replaced by other radicals.

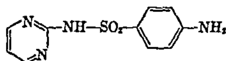
There are a large number of other antibiotics known and the number is growing constantly. Many of these are too toxic to be of value. Others that have found a place in medicine are aureomycin, chloromycetin (p. 685), streptomycin, and tyrothricin.

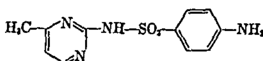
Sulfa Drugs. Although the popularity of these drugs declined markedly after 1945 as antibiotics, such as penicillin, streptomycin, and chloromycetin, became available, they still are prescribed in many cases. The danger of kidney damage, owing to their low solubility in water and resulting tendency to crystallize, is greatly reduced by the use of mixtures. They may have other bad effects, such as decrease of white blood cells, fever, rash, and acidosis. They are effective against many streptococcal infections, also gonococcal infections. A general method for their preparation is the action of p-acetamidobenzenesulfonyl chloride on an amino compound, as in the case of sulfapyridine. The product, N-acetyl-N′-pyridylsulfanilamide, is heated with dilute hydrochloric acid to remove the acetyl group and the desired product is precipitated by removal of hydrochloric acid.

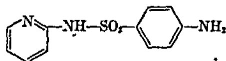


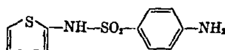
sulfapyridine
N′-2-pyridylsulfanilamide

The most important of the sulfa drugs are sulfanilamide (p. 479), sulfadiazine, sulfamerazine, sulfapyridine, and sulfathiazole. Interesting also are prontosil, the first sulfanilamide derivative to be used clinically, and neoprontosil, a more soluble compound. These are red dyes that undergo scission in the animal body to sulfanilamide.


sulfadiazine


sulfamerazine


sulfapyridine


sulfathiazole

Sulfapyridine is effective against pneumonia and was the first drug to be used for this purpose. It is usually more toxic than sulfanilamide. It is now largely supplanted by sulfadiazine and sulfathiazole, for these are less toxic, and also more potent against most disease organisms. With the exception of some staphylococcal infections, for which sulfathiazole is more effective, sulfadiazine is the preferred sulfa drug, because of its lower toxicity.

p-Aminobenzoic acid, an essential growth factor for most of the bacteria that are affected by sulfonamide drugs, exerts an antagonistic effect when administered in small amounts along with these drugs. It is believed that sulfanilamide and its N′-substituted derivatives substitute for *p*-aminobenzoic acid in the metabolism of bacteria. This causes a decrease in their rate of growth and reproduction, since the sulfur compounds cannot perform the function of *p*-aminobenzoic acid. However, if the latter is administered with the drug, the organisms can obtain sufficient aminobenzoic acid for continued growth, and thus it counteracts the effect of the drug.

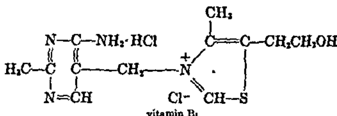
HETEROCYCLIC VITAMINS

At one time (1915) two types of accessory factors in nutrition were recognized, *viz.*, "Fat-Soluble A" and "Water-Soluble B." The former was shown to be a cure for a nutritional eye disease, and the latter, for beriberi. Later it was recognized that a number of vitamins are included in the two groups; in the fat-soluble group, vitamins A (p. 649) and E, and in the water-soluble group, thiamin (vitamin B_1), riboflavin (vitamin B_2), pantothenic acid (vitamin B_3?, p. 590), nicotinic acid (vitamin B_5?), pyridoxin (Vitamin B_6), inositol, *p*-aminobenzoic acid (p. 535), and perhaps others.

Two well-recognized diseases resulting from deficiencies of the vitamin B complex are beriberi and pellagra. Some of the effects of beriberi are lassitude, polyneuritis, cramps, lameness, and enlargement of the heart; of pellagra, lesions of the skin and mucous membranes and finally lesions of the central nervous system. Vitamin B_1 is the antiberiberi vitamin and nicotinic acid and nicotinic amide constitute the Pellagra Preventive factor. How-

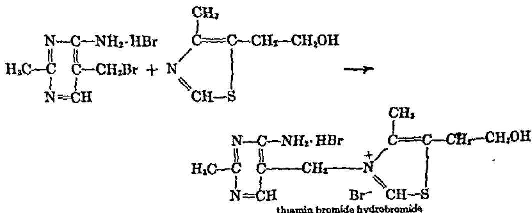
ever, other B vitamins are involved, and sometimes administration of one or more of these is required, for example, riboflavin and pantothenic acid for beriberi and pellagra, thiamin and pyridoxine for pellagra.

Vitamin B_1, Thiamine Chloride, $C_{12}H_{17}ON_4SCl \cdot HCl$. Lack of this vitamin produces the symptoms of beriberi. The vitamin is found in small amounts in many vegetable products. Among the best sources are yeast and wheat germ. It is isolated usually as a salt with hydrochloric acid. It has a pyrimidine ring system attached to the nitrogen atom of a thiazole ring system so as to form a quaternary ammonium salt.



vitamin B_1

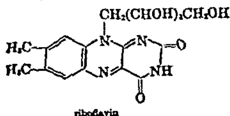
The bromide hydrobromide of thiamin has been synthesized by heating the hydrobromide of 6-amino-5-bromoethyl-2-methylpyrimidine with 5-β-hydroxyethyl-4-methylthiazole (p. 670).



thiamin bromide hydrobromide

This is converted into the corresponding chlorine compound when its aqueous solution is shaken with silver chloride.

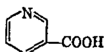
Vitamin B_2, Riboflavin, Lactoflavin, Dimethylribityl-iso-alloxazine, $C_{17}H_{20}O_6N_4$: This is a constituent of all cells. It has an *ortho*-xylene ring fused to a partially reduced pyrazine ring and this is fused to a uracillike ring. To the middle ring is attached a D-ribityl group, which in nature is esterified at the terminal position with phosphoric acid.



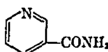
riboflavin

Riboflavin is widely distributed in plants and animals. The richest sources are liver, kidney, heart, and anaerobic growing fermentation bacteria. It is essential for growth. It takes part in the enzyme systems that regulate oxidations taking place in cells.

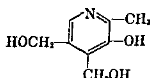
Nicotinic Acid, Niacin, m.p. 234°, $C_6H_5O_2N$; Nicotinamide, Niacin amide, m.p. 122°, $C_6H_6ON_2$; Vitamin B_5?. Nicotinic acid, in the form of nicotinamide, is present in all living cells. The amount is small. The amide is mainly combined in enzyme systems that are important in oxidation-reduction reactions. Deficiency of nicotinic acid, nicotinamide, or sometimes of other B vitamins may lead to the symptoms of pellagra. These usually are relieved by the addition of niacin or niacinamide to the diet; but sometimes one or more other B vitimins must be administered, for example, thiamine or pyridoxine.



nicotinic acid



nicotinamide

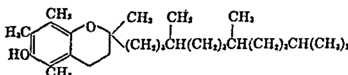


pyridoxine

Vitamin B_6, Pyridoxine, 3-Hydroxy-4,5-dimethylol-2-methylpyridine, $C_8H_{11}O_3N$, m.p. 210–217°. This is present only to a slight extent in the free state and is mostly combined with protein. It is widely distributed in plants and animals, and is especially plentiful in yeast, rice polishings, and seeds and cereals. The vitamin is essential for growth of rats and its deficiency produces abnormal conditions in other animals. Phosphorylated pyridoxine is the coenzyme of amino acid decarboxylases and transaminases. It is codecarboxylase.

Pyridoxal and pyridoxamine are related compounds in which the 4-methylol group is replaced by the aldehyde and aminomethyl group, respectively. Vitamin B_6 is a complex of pyridoxine, pyridoxal, and pyridoxamine.

Vitamins E, Tocopherols. These are three closely related compounds, *viz.*, α-, β-, and γ-tocopherol, that stimulate reproduction. They sometimes are called the antisterility vitamins. They occur mainly in plant oils. Wheat germ oil is one of the best sources. They have a tetrahydrobenzopyran nucleus and a long side chain.



α-tocopherol

In β-tocopherol the 7-methyl group is lacking and in γ-tocopherol the 5-methyl group. The tocopherols have been synthesized. Trimethylhydroquinone and phytyl bromide, in the presence of zinc chloride and with benzene as the solvent, give DL-α-tocopherol in almost quantitative yield.

CHAPTER 46

Synthetic Dyes

The art of dyeing fibers was known to the ancients and has been practiced by most primitive peoples. They learned how to extract highly colored products from plants and to apply these to various fabrics so as to make them more attractive. Two of the most prized colors were the blue of indigo (p. 716), and the red of madder (p. 574). These and most other natural colors have been synthesized. Generally, the synthetic product can be produced more economically than the natural. Thus, their production from plants declined decades ago, and by now has virtually ceased. The large tracts of land formerly devoted to the culture of plants for natural dyestuffs production are now given over to the raising of foodstuffs, fibers, or other products.

Surprisingly enough, the first commercially successful synthetic dye was not a naturally occurring one. In 1856 William H. Perkin, while attempting a synthesis of quinine by the oxidation of crude aniline, obtained a substance which dissolved with a brilliant violet color and dyed silk and wool. This was called mauve by its discoverer (then only 18 years of age), who, against the advice of his teacher, Hofmann, went into the business of manufacturing this dye. The venture was successful and in time came to include the manufacture of similar dyes discovered subsequently. The year 1856 also marked the discovery by Natanson of the brilliant red dye, rosaniline (fuchsine, magenta), a triphenylmethane dye. At first the development of synthetic dyes of this type was more or less empirical, since this was before Kekulé proposed the ring structure for benzene (1866). The first azo dye, aniline yellow, was discovered by Mêne in 1861, but more than a decade elapsed before the investigation of this latter field was carried on vigorously. The structure of alizarin, the dye from madder, was solved in 1868 by Graebe and Liebermann, and that of indigo in 1882 by Baeyer. Both alizarin and indigo are now produced synthetically.

Color. Color is one manifestation of light, and light is one form of electromagnetic radiation. There are a number [illegible] of electromagnetic radiation. These all have the [illegible] veloc[illegible] of light, 186,000 miles (2.99796×10^8 meters[illegible] bu[illegible] length and frequency. Radiation of longer [illegible] a[illegible] than one of shorter

wave length. Wave lengths in meters cover a wide range. Ordinary broadcast radio waves are 3×10^2 meters and gamma radiation about 10^{-12} meters. The units usually employed for wave lengths in the visible and adjoining regions of the spectrum are: the Ångstrom ($1\ \text{Å} = 0.1\ \text{m}\mu = 10^{-8}\ \text{cm} = 10^{-10}\ \text{m}$) and millimicron ($1\ \text{m}\mu = 10^{-7}\ \text{cm} = 10^{-9}\ \text{m}$). Visible light lies between about 7600 Å and about 4000 Å. Beyond the longer wave length side is the infrared, and beyond the shorter wave length side, the ultraviolet. Infrared radiation has a lower frequency than visible light, and ultraviolet has a higher frequency.

Radiation is a form of energy. A relationship, in terms useful for regions near the visible part of the spectrum, states that the product of λ, the wave length in Ångstrom units, and E, the energy of the quantum which is characteristic of that particular wave length, is 12,395, according to the first equation below. The second equation is an expression of the energy, $\bar{E}$, in terms of kcal. per mole, that is, the energy of one mole of quanta.

$$\lambda E = 12{,}395 \qquad \bar{E} = (12{,}395/\lambda)23.07\ \text{kcal./mole}$$

A substance is colored if it absorbs light in the visible region; thus the color which the eye records is not the color of the light absorbed but the complementary color. Two colors are complementary if they produce white, when blended in the proper proportions. In Figure 39 are shown the spectrum colors so arranged that complementary colors are opposite each other. It is seen that greenish yellow is complementary to violet, red to blue-green, etc.

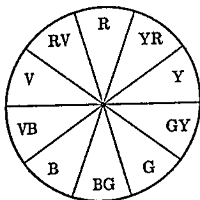


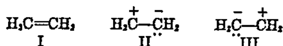
Figure 39 · The Color Wheel.

Absorption of electromagnetic radiation produces dark lines in the spectra of simple substances such as gaseous atoms. These are the well-known Fraunhofer lines in the spectra of the elements. Organic molecules, even those that are colorless to the human eye, absorb radiation. That absorbed by a colorless compound can be in the infrared or the ultraviolet. Evidence of such absorption usually can be obtained by spectroscopic methods.

Absorption in the visible region by a colored organic substance can be observed visually by allowing white light to pass through a solution of the colored substance then through a prism. The prism separates white light into the spectral colors. The absorption bands appear as dark regions.

Energy is taken up by a substance when it absorbs radiation, and this per molecule is the quantum of energy characteristic of the particular wave length of the radiation. The relatively small energy changes that attend absorption in the far infrared, namely, longer than 30,000 Å, are associated with the fundamental rotational and vibrational frequencies. A molecule rotates or vibrates more rapidly, as a result of acquiring a small quantum of energy

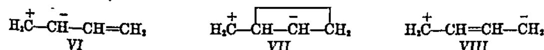
energy between the ground state and the first excited state with each additional double bond is largely the result of resonance. Thus for ethylene the main contribution to the ground state is made by only one structure, I, and to the first excited state, by the two ionic (dipolar) forms, II and III.



For butadiene, two structures, IV and V, make the main contribution to the ground state, and twelve singly ionized structures to the first excited



state. There are four positions for the positive ion (the four carbon atoms) and for each of these there are three positions for the negative ion, making twelve in all. The possibilities are shown in one case by VI, VII, and VIII.



As a result of the contribution of these twelve singly ionized forms and possibly of others to the first excited state of butadiene, the stabilization resulting therefrom leads to a lower activation energy than is true of ethylene, and a consequent longer wave length of light absorbed. A similar explanation applies to hexatriene and octatetraene. In these cases, the longer the conjugated chain the greater the excess stabilization of the first excited state through resonance, in comparison to that of the ground state.

Organic dye molecules contain aromatic ring systems. The attachment of a conjugated system to one of these resonating aromatic systems is especially effective in producing color. Nitrobenzene has a pale yellow color, but nitromethane is colorless. Of the diphenylpolyenes, $C_6H_5(CH{=}CH)_nC_6H_5$, stilbene, $n = 1$, is colorless and 1,6-diphenyl-1,3,5-hexatriene, $n = 3$, is yellow-green. *Thus the absorption band of 1,3,5-hexatriene is shifted into the visible* part of the spectrum by the two benzene rings, whereas the unsubstituted triene absorbs only in the ultraviolet (p. 700).

The intensity of light absorption is raised through resonance, probably because more molecules become activated and the absorption bands are widened. This is due to the fact that in any one state, for example, the ground state, there are numerous slight differences in energies among the molecules. These may arise from differences not only in rotational and vibrational energies, but also in the energies of the different resonance forms contributing to that state. Thus the quanta that can cause excitation from this state to a particular excited state will have a wider energy range, because of the many different combinations for excitation. Resolution of many bands has shown them to be made up of numerous absorption lines, closely spaced.

The Chromophore Theory. In 1876 Witt proposed a theory of color that has greatly aided the development of dye chemistry. Colored substances are called **chromogens**; in general, chromogens possess slight if any dyeing power. A chromogen owes its color to the presence of a color group, called a **chromophore.** In order to be a dye, there must also be in the molecule an acidic or basic group, called an **auxochrome.** The nitro, azo, and carbonyl groups were the chromophore groups recognized by Witt.

The most common of the chromophores are: (1) nitroso; (2) nitro; (3) azo; (4) azoxy; (5) diketo; and (6) conjugated systems. It will be recalled that nitrosobenzene in solution is green, nitrobenzene is a pale yellow, azobenzene is red, azoxybenzene is orange, biacetyl is a pale yellow, and carotene is a deep red. The systems characteristic of quinones are essentially diketones in which a conjugated chain separates the two carbonyl groups. Thus 1,4-benzoquinone, 1,4-naphthoquinone, and anthraquinone are yellow, while 1,2-benzoquinone and 1,2-naphthoquinone are red, and phenanthraquinone is orange. It should be noted that the oxygen atoms of a quinone can be replaced by other atoms and still the compound can be colored, for example, a quinoneimine. Thus the structure characteristic of a quinone is sometimes considered to be a chromophore. It should be noted that all of the chromophores just mentioned contain one or more unsaturated linkages.

The most effective auxochromes are: (1) hydroxyl; (2) amino; (3) monosubstituted amino, and (4) disubstituted amino groups. Less effective are (5) carboxyl and (6) sulfonic acid groups. There are two effects of the auxochrome when it is an amino (alkyl amino) or hydroxy group attached to an aromatic ring: (1) the color is greatly intensified and (2) the substance can be fixed on fibers.

A dye that has in its structure an amino or alkyl amino group is a **basic dye** and forms salts with strong acids. A dye that has a phenolic hydroxyl, a carboxyl, or sulfonic acid group is an **acid dye** and forms salts with bases. A dye having both an amino and sulfonic acid group is an acid dye because the sulfonic acid group is strongly acidic, whereas the amino group, especially when attached to an aromatic ring, is only weakly basic.

The intensification of color that results from the presence of an auxochrome group in a molecule having also a chromophore group is now explained as resulting largely from resonance. The stabilization of electronically excited states is so great that the absorption can be quite extensive in the visible region of the spectrum.

Classification of Dyes on a Usage Basis. The main use of dyes is in the textile industry, for the dyeing of fabrics. Other applications of dyes are found in the manufacture of inks, lakes, and pigments, the coloring of gasolines, the coloring of foods (a limited number, approved by the Federal Government), and the sensitizing of photographic films. Dyes used for the coloring of gasoline, as well as those for the dyeing of some of the synthetic fabrics, are known as oil soluble dyes.

There is a marked difference in the ease with which fabrics can be dyed.

Those of animal origin are the most easily dyed since they are composed largely of protein and have free amino and free carboxyl groups. These include wool, silk, hair, and leather. Cellulosic materials, such as cotton, linen, and rayon take dyes less readily, since they lack acidic or basic groups. Some synthetic fibers are even less readily dyed.

Dyes are said to be fast dyes when they retain their color, by showing resistance to washing of the fabric, and resistance to the combined effects of light and air. Fastness to washing is related in part to insolubility of the dye in water, and fastness to light is related in part to the resistance of the dye to oxidation.

In the textile industry, dyes are classified largely on the basis of the dyeing process, for example, acid dyes, basic dyes, ingrain dyes, substantive dyes, mordant (and mordant azo) dyes, vat dyes, sulfur dyes, and dispersed dyes.

Acid dyes. Animal fibers are dyed directly in a bath of a salt of an acid dye. This may be one having a phenolic hydroxy group, or a carboxylic or sulfonic acid group. One of the simplest acid dyes is picric acid.

Basic dyes. Animal fibers can be dyed directly in a bath of a salt of a basic dye. Usually the color must be fixed by means of a suitable acid mordant, that is, one that forms with the dye an insoluble colored compound, a so-called lake. A common mordant is a combination of tannic acid with an antimony salt, for example, tartar emetic. Phosphotungstic and phosphomolybdic acids also are important mordants. Basic dyes are not nearly so important as formerly and are continually losing ground to other types.

Ingrain dyes. These are often called "ice colors." They are insoluble azo dyes produced by the coupling of a diazotized amine with an aromatic amine or phenol (usually naphthol). After the fiber has been impregnated with the amine or phenol it is passed into a bath containing the diazonium salt. The dye is formed within the fiber. By varying the nature of the amine to be diazotized and also the coupling compound, a very large number of azo dyes can be made. The more valuable ones are disazo or more complicated ones. Formerly the diazotization process was carried out cold, hence the name "ice colors," but now many stable diazonium salts are available. In these the negative ion is usually a sulfonic acid, as for example naphthalenesulfonic acid. Naphthols and aromatic bases are much more readily absorbed by cellulose acetate than by cellulose. Since these are taken up so much more readily by cellulose acetate, it is possible to dye a mixed fabric of cotton and cellulose acetate, and leave the former nearly white.

Sometimes both the amino and phenolic compounds are absorbed by the fiber first. Then on the addition of nitrite the amine is diazotized within the fiber and also coupling takes place within the fiber.

Substantive (direct) dyes. These have the ability to dye cotton directly. The original substantive dye is Congo red (p. 707). Many other direct dyes are made from derivatives of benzidine. They have two or more azo groups and one or more sulfonic acid groups, and are used in salt form, usually as the sodium salt.

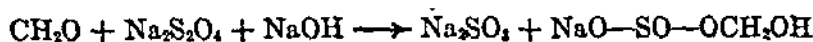
Mordant dyes. These are soluble acid dyes that do not dye the fiber directly, but need to be fixed on the fabric with a basic mordant. This is the salt of a metal with a weak acid, for example, acetic acid, which when heated with the dye forms an insoluble compound, a lake (p. 714). Aluminum, chromium, and iron salts are the common mordants. The mordant can be incorporated with the dye in a printing paste, which is applied to the fabric. On steaming, the lake is formed on the fabric. The classical example of a mordant dye is alizarin. *Chromation* is mordanting with a chromium salt produced *in situ* by reduction of a soluble chromate.

Often a fabric already dyed by some other process, as for example with a substantive or ingrain dye, is immersed in a bath of a suitable metallic salt. Absorption of the metallic ion by the dye produces a faster color. Also, the brightness of the color usually is improved.

An important area of usefulness for dyes is in the pigment field. Organic pigments are combinations of acid dyes with basic mordants, or of basic dyes with acid mordants. These are faster colors than the dyes themselves, and usually are more brilliant. An important use of pigments is in printing.

Vat dyes. These are insoluble dyes, often of rather high molecular weight and usually very fast. They are rendered soluble by reduction to a phenolic or enolic form, often called the "vat." The fiber may be dyed by immersion in a vat of the reduced dye, usually heated, or by means of a thick paste containing the dye and a reducing agent as well as other components. The paste is printed on the fiber and steamed for some time in the absence of oxygen, to bring about reduction and fixation of the reduced dye on the fiber. By action of air or other oxidizing agent the original color is re-formed (developed). Important vat dyes are the indigoids and many derivatives of anthraquinone, in particular, the indanthrenes.

The usual reducing agent for vat dyeing is sodium hydrosulfite (dithionite, $Na_2S_2O_4$) and for paste dyeing, sodium sulfoxalate formaldehyde. This is prepared from formaldehyde, sodium hydrosulfite, and sodium hydroxide.



$$CH_2O + Na_2S_2O_4 + NaOH \longrightarrow Na_2SO_3 + NaO{-}SO{-}OCH_2OH$$

Sulfur dyes. These are high molecular weight insoluble dyes of good fastness. They are made by heating various organic compounds with sulfur or an alkali sulfide or both. Dyeing is similar to vat dyeing

Dispersed dyes. Some of the synthetic fibers, for example, cellulose acetate and nylon, absorb certain dyestuffs by a process that is akin to solubility. Such colors in many cases are insoluble in water. They are put into a highly dispersed state, after thorough grinding, with water soluble dispersing agents. Absorption by the fiber may be fairly slow.

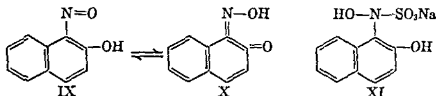
Classification of Dyestuffs on a Chemical Basis. There are numerous classes of dyes (see the *Colour Index*, Society of Dyers and Colourists, Bradford, Eng., 1924). Some of the classes mentioned below are selected, either because of their simple structure or their importance industrially, or from a theoretical standpoint. A relatively few examples are taken from these

classes: (*a*) nitro and nitroso dyes; (*b*) azo dyes; (*c*) diphenylmethane dyes; (*d*) triphenylmethane dyes; (*e*) anthraquinone dyes; (*f*) indigoid dyes; (*g*) xanthene dyes; (*h*) quinoline dyes; (*i*) aniline black; (*j*) sulfide colors; (*k*) phthalocyanines.

NITRO AND NITROSO DYES

The nitro dyes usually are nitrated phenols, sometimes nitrated amines They are of relatively little importance industrially, because the colors are not very fast. Examples are **picric acid,** 2,4,6-trinitrophenol, **naphthol yellow** (Martius yellow), 2,4-dinitro-1-naphthol, and **naphthol yellow S,** the potassium (or sodium) salt of 2,4-dinitro-1-naphthol-7-sulfonic acid. The last is one of the colors permitted in foods.

An example of a nitroso dye is **gambine,** 1-nitroso-2-naphthol, IX (or β-naphthoquinone monoxime, X), obtained by the action of nitrous acid on β-naphthol. This is employed in the form of the bisulfite addition compound, XI.



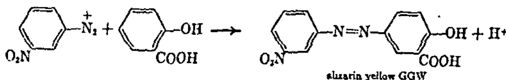
It is a fast dye and dyes cotton a fast green with ferric iron as the mordant

AZO DYESTUFFS

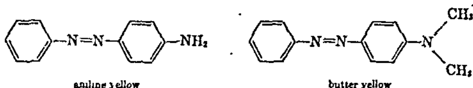
The principal types are hydroxyazo, aminoazo, or N-substituted aminoazo compounds, and are produced by the coupling of diazonium salts with phenols (naphthols) or aromatic amines (Chaps. 32, 38). They may be derived from benzene, naphthalene, anthracene, or other aromatic hydrocarbon or aromatic heterocyclic system. The aminoazo compounds are basic, some hydroxyazo compounds are acidic, and the N- or O-acylated derivatives are neutral. Azo dyes made with β-naphthol are essentially neutral, provided the molecule does not have some other group that is either acidic or basic. Often one or more sulfonic acid groups are present in the molecule. The function of these is to impart water solubility to the dye, usually in the form of a salt, as for example, a sodium salt, and also to aid in the fixing of the dye on the fiber.

Azo dyestuffs may be applied to the fiber in different ways: (1) by the ingrain process; (2) directly, in which case they often are given a subsequent treatment with a metallic salt, for example, chromium, to increase fastness; (3) mordant azo dyes. These last have two functional groups so arranged, usually *ortho* to each other, that one can enter into salt formation with the metal and the other can form a coordination link. This is possible if the hydroxyl function of a hydroxyazo dye is *ortho* to the azo group or if a carbonyl function is *ortho* to a hydroxyl function. This last arrangement is character-

istic of salicylic acid. Many mordant azo dyes are made with salicylic acid as one of the components. An example is alizarin yellow GGW, made from diazotized *m*-nitraniline and salicylic acid.

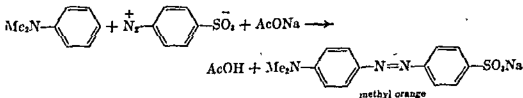

alizarin yellow GGW

Aniline Yellow, *p*-Aminoazobenzene Hydrochloride. This is the simplest basic azo dye (p 490). It will dye silk and wool but the color is fugitive. Its main use is in the preparation of disazo dyes. It is prepared by the rearrangement of diazoaminobenzene. **Butter yellow**, dimethylaminoazobenzene, is prepared by the reaction of benzene diazonium chloride with dimethylaniline. It and aniline yellow base are oil soluble.

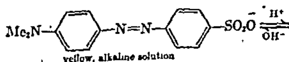

aniline yellow butter yellow

Bismarck Brown. This is formed by the action of nitrous acid on *m*-phenylenediamine. The diazonium compound first formed couples with the unchanged diamine. The product is a mixture of azo and disazo compounds. Bismarck brown is used for the dyeing of leather. The reaction which produces the dye can serve as a test for nitrous acid or nitrites.

Methyl Orange, Helianthine, Sodium 4-Dimethylaminoazobenzene-4′-sulfonate. It is prepared by the reaction of dimethylaniline with diazotized sulfanilic acid.

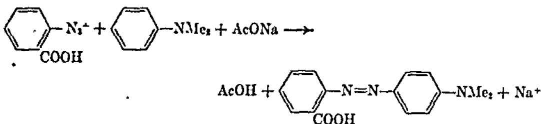

methyl orange

Methyl orange is not a satisfactory dye because it is not fast and because the color changes when acid is added. It is this property of changing color over a small *p*H range, namely 3.2 to 4.4, that makes it a good indicator; orange-yellow in alkaline solution, red in acid solution. The change in color is caused by a change ... ture; under alkaline conditions the compound has the s... an azo co... der acid conditions that of a quinonediimine.


yellow, alkaline solution

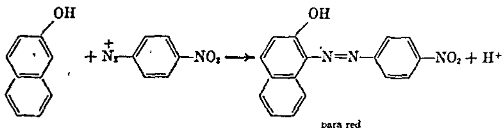
$e_2\overset{+}{N}$—

Methyl Red, 4-Dimethylaminoazobenzene-2′-carboxylic Acid. This is prepared *from dimethylaniline and diazotized anthranilic acid.*



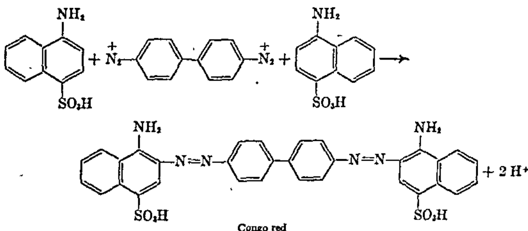
The color change over the *p*H range, 4.4 to 6.2, is more pronounced than that of methyl orange.

Para Red, *p*-Nitrophenylazo-*β*-naphthol. This is a good example of an ingrain color. The fiber is impregnated with *β*-naphthol by immersion in an alkaline solution of *β*-naphthol. Then it is dried and the dye is produced by contact with a solution of *p*-nitrobenzenediazonium chloride, followed by addition of a solution that reduces the acidity, for example, sodium acetate or sodium carbonate.



para red

Congo Red. This is the first of the substantive dyes, and is obtained by the coupling of diazotized benzidine with naphthionic acid

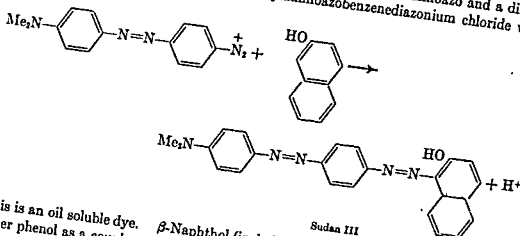


Congo red

Congo red is sensitive to acids, and changes to blue at approximately *p*H 3. It is sometimes used to indicate the point at which addition of a strong mineral acid, hydrochloric acid, for example, has caused decomposition of a salt of a weak acid such as sodium acetate.

Congo red is not a satisfactory dye, on account of its sensitivity to acids. However, many derivatives, also disazo compounds, are satisfactory dyes, for example. **benzopurpurin 4B.** This is a dimethyl derivative and is prepared from naphthionic acid and diazotized *o*-toluidine (4,4′-diamino-3,3′-dimethylbiphenyl).

Sudan III. This is an example of a dye that is both an aminoazo and a disazo dye. It is prepared by coupling dimethylaminoazobenzenediazonium chloride with β-naphthol.

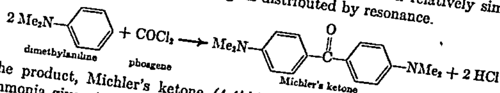


Sudan III

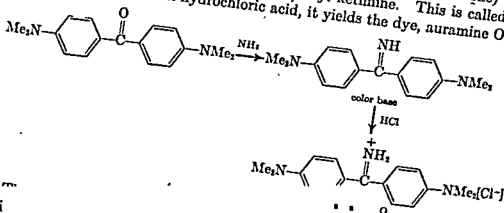
This is an oil soluble dye. β-Naphthol (including derivatives) is used more than any other phenol as a coupling agent.

DIPHENYLMETHANE DYES

Auramine O. This is one of the simpler diphenylmethane dyes and is also one of the most valuable of the basic dyestuffs used in the paper industry. It is usually classified as a ketimine dye. It can be prepared from phosgene and dimethylaniline. It is described here because it is a relatively simple example of the way an ionic charge is distributed by resonance.

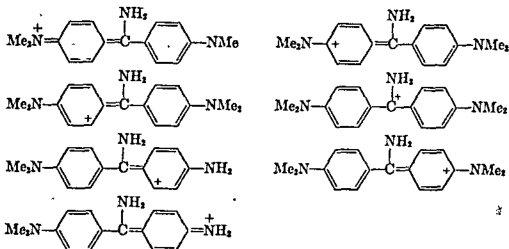


The product, Michler's ketone (4,4′-bisdimethylaminobenzophenone) with ammonia gives 4,4′-bisdimethylaminodiphenyl ketimine. This is called the color base because, with hydrochloric acid, it yields the dye, auramine O.



T... O is a resonance hy-
bri... ...ms. The positive charge is not localized on
the ...imine nitrogen atom but is distributed between all of the nitrogen
atoms. In order for this distribution to take place, the positive charge is

believed to pass along the carbon chain, as a result of contributions of other resonance forms, in addition to the one shown above.

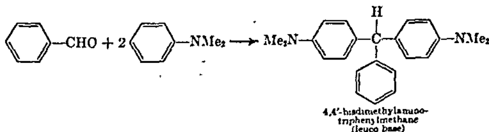


There are other resonance forms, not shown, that arise from other Kekulé structures. As a result of these, the greatest contribution to the overall structure is made by those forms in which the ketimine nitrogen atom or the methane carbon atom carries the positive charge.

The intense color of the dye is related to the existence of the many forms that permit of the distribution of the positive charge. In the ground state there are three principal energy levels, corresponding respectively to (1) two benzene rings, (2) one benzene ring and one *p*-quinone ring, and (3) one benzene ring and one *o*-quinone ring. In addition, there are minor differences, the result of rotational and vibrational energies. Similar statements apply to the excited states. Thus the factors that are responsible for the absorption of radiation in the visible region are accentuated when the charge on an ion is distributed by resonance.

TRIPHENYLMETHANE DYES

Malachite Green. This is one of the simpler of the triphenylmethane dyes. Its preparation, by the condensation of benzaldehyde with dimethylaniline, illustrates a general method of preparation. The reagents are heated in the presence of a condensing agent. Zinc chloride was formerly used, but hydrochloric acid is now preferred.



4,4'-bisdimethylaminotriphenylmethane (leuco base)

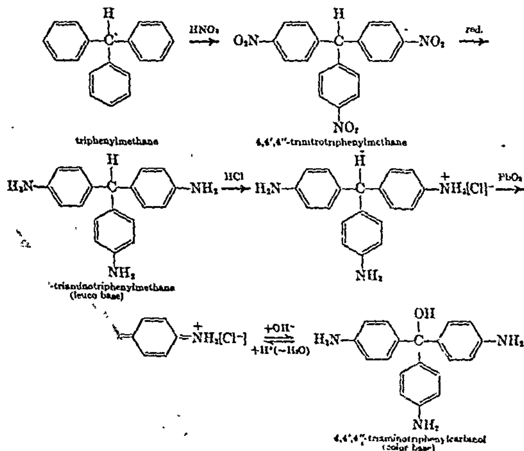
The intense color of malachite green, like that of auramine O (p. 708), is due to the distribution of the positive charge, as a result of resonance. Neglecting the intermediate carbonium ion forms, the extreme forms have the positive charge on the nitrogen atoms. Addition of hydrochloric acid in excess causes the color to fade to a pale yellow. This is due to salt formation at the second basic group. As a result, the resonance shown (p. 710) does not take place. Thus the intense color is destroyed, but the dihydrochloride is still colored because of the quinoid ring.

Brilliant Green. This is similar to malachite green in structure except that it is prepared from diethylaniline, instead of dimethylaniline. It is a more intense green.

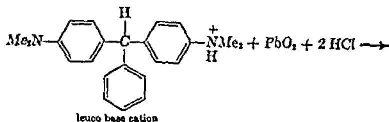
Setoglaucine. This is similar to malachite green except that it is prepared from o-chlorobenzaldehyde, instead of benzaldehyde. It is a brilliant greenish blue. Its main use is in the manufacture of pigments, for example, permanent peacock blue.

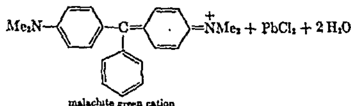
Pararosaniline, Paramagenta, $C_{19}H_{18}N_3Cl$. This is generally prepared by a reaction between aniline, p-toluidine, and a mild oxidizing agent under acid conditions (p. 712). Its preparation from triphenylmethane confirms the structure established by its conversion to triphenylmethane.

Nitration of triphenylmethane yields 4,4′,4″-trinitrotriphenylmethane, reduction of this gives 4,4′,4″-triaminotriphenylmethane (the leuco base), and mild oxidation of this under acidic conditions, as with lead dioxide, yields an intense magenta-colored solution, that of the dye.

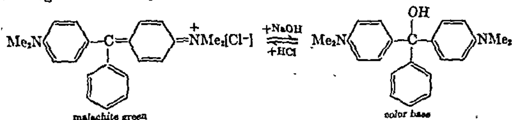


The product, 4,4′-bisdimethylaminotriphenylmethane is essentially insoluble in water, soluble in dilute hydrochloric acid. If pure, and if oxygen is excluded, the resulting solution is colorless. On this account the compound is called a **leuco base**, to signify that it does not give a colored salt. Addition of a suitable oxidizing agent (preferably freshly prepared lead dioxide) to the solution causes an intense green color. This involves oxidation of the leuco base and development of a quinoid structure.

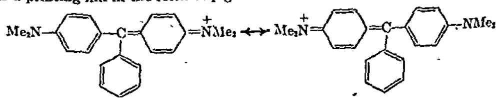




Addition of sodium sulfate removes lead ions as insoluble lead sulfate. Then the **color base**, 4,4′-bisdimethylaminotriphenylcarbinol, is precipitated as an amorphous product, colorless when pure, by the addition of sodium carbonate or sodium hydroxide. Addition of hydrochloric acid or other strong acid regenerates the dye.



The dye can be obtained in crystalline form by reaction of the color base with aqueous oxalic acid. The oxalate, $2\ C_{23}H_{24}N_2 \cdot 3\ C_2H_2O_4$, crystallizes nicely from a hot solution when the temperature is allowed to drop very slowly. Another crystalline form of the dye is obtained by adding zinc chloride and sodium chloride to the hydrochloric acid solution of the dye. This gives a slightly soluble double salt of the dye with zinc chloride, $3\ C_{23}H_{25}N_2Cl \cdot 2\ ZnCl_2 \cdot 2\ H_2O$, which formerly was the usual commercial product. Malachite green is used as a printing ink in the form of pigments.



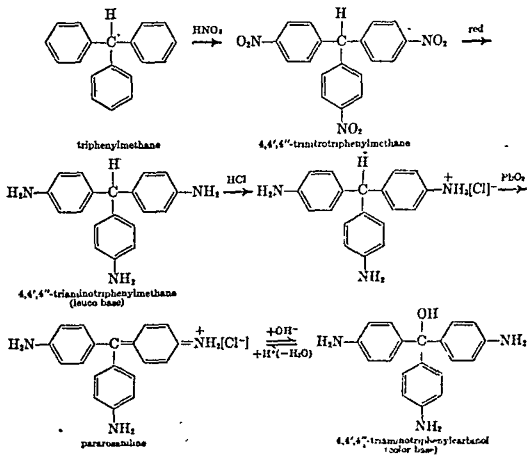
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Pararosaniline is soluble in water, forming a rose-colored solution. It dyes wool and silk directly, but the colors are fugitive. Distribution of the positive charge, as the result of resonance, is considered to be the cause of the intense color (see Auramine O and Malachite Green).

As shown by the last equation, the addition of base to a solution of the dye causes the formation of the leuco base, as it does with malachite green, and the leuco base is precipitated, owing to its insolubility. Addition of hydrochloric acid to the color base redissolves it, with formation of the dye.

Excess of hydrochloric acid causes a fading of the magenta color to yellow, except that more acid is needed than in the case of malachite green. This is because all three amino groups must be in salt form before resonance involving shifting of the positive charge is suppressed.

Pararosaniline usually is produced by a reaction first used for preparing it. A mixture of aniline and p-toluidine with hydrochloric acid is heated with a mild oxidizing agent (arsenic acid; nitrobenzene with iron or ferrous chloride).

$$H_2N\text{-}C_6H_4\text{-}H + H\text{-}CH_2\text{-}C_6H_4\text{-}NH_2 + H\text{-}C_6H_4\text{-}NH_2 + 3\,[O] + HCl \longrightarrow$$

$$H_2N\text{-}C_6H_4\text{-}C(C_6H_4NH_2){=}C_6H_4{=}\overset{+}{N}H_2[Cl^-] + 3\,H_2O$$

pararosaniline

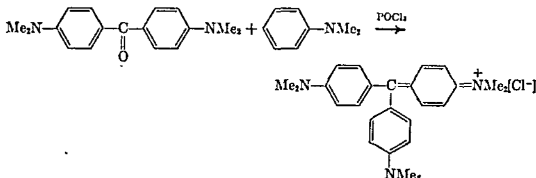
A single compound is not formed, since some ortho-positions may be involved. Also, two toluidine and one aniline molecule may react. The dye is a mixture.

The structure of the dye prepared by this reaction was partially established by conversion of the dye, in steps, to triphenylmethane: first, the color base was obtained by the addition of alkali; second, this was reduced to triaminotriphenylmethane; and third, this, when diazotized and boiled with alcohol, was reduced to triphenylmethane.

$$\underset{\text{color base of pararosaniline}}{(H_2NC_6H_4)_3COH} \longrightarrow \underset{\text{leuco base of pararosaniline}}{(H_2NC_6H_4)_3CH} \longrightarrow \underset{\text{diazotized leuco base}}{(ClN_2C_6H_4)_3CH} \longrightarrow \underset{\text{triphenylmethane}}{(C_6H_5)_3CH}$$

a mixture of sodium chloride, cupric sulfate, and phenol. The dye is the hydrochloride salt. It gives an intense violet color in water. Replacement of the hydrogen atoms of the amino groups of pararosaniline by methyl groups shifts the color from red to bluish-violet. Ethyl groups have a similar and stronger effect in this direction, and phenyl groups, even more so.

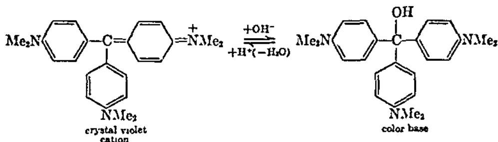
Crystal violet is obtained when Michler's ketone (p. 708), dimethylaniline, and phosphorus oxychloride are heated. The carbinol base probably is an intermediate



Dimethylaniline and phosgene alone will produce the dye, since these two react to give Michler's ketone.

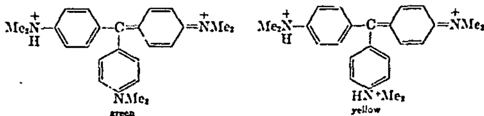
The dye usually is the hydrochloride salt. It can be obtained as well-defined crystals having a greenish-brown metallic luster. It is soluble in water or alcohol with a deep violet-blue color, somewhat more blue than the color of methyl violet.

Addition of a base to a solution of crystal violet causes the formation of the insoluble color base, 4,4',4''-trisdimethylaminotriphenylcarbinol. This with an equivalent amount of hydrochloric acid is reconverted to the soluble dye.



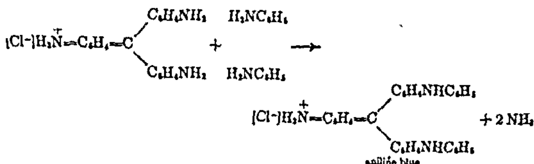
On the addition of more hydrochloric acid, crystal violet becomes green, and with still more, yellow.

The intense color of crystal violet is explained on the basis of distribution of the positive charge of the dye cation among three equivalent nitrogen atoms. When a second equivalent of acid has entered into combination, two of the basic nitrogen atoms carry a positive charge. The green color at this stage is a result of the type of resonance characteristic of malachite green. When all three groups are in salt form, the yellow color is due to the quinoid ring.



Ethyl Violet, Ethyl Purple, Hexaethylpararosaniline Chloride. This is made from phosgene gas and diethylaniline. *It is similar in most properties to crystal violet, except that its color is purple.*

Aniline Blue. *This is prepared from* pararosaniline by heating it at 180° with aniline and benzoic acid; the acid acts as a condensing agent. *The dye is a mixture of* different phenylated products, including the triphenyl compound.



The effect of the additional phenyl groups is a pronounced shift in color towards the blue.

ANTHRAQUINONE DYES

There are two main types of anthraquinone dyestuffs, *viz.*, mordant dyestuffs and vat dyestuffs. A typical example of the former is alizarin (p. 574), and of the latter, algol red. Vat dyes have become of relatively greater importance during the past few decades, owing to their greater insolubility and fastness.

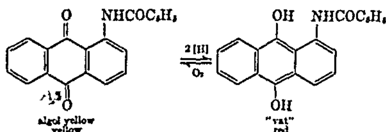
The mordant dyes are generally acid dyes, the acid property being associated with the presence of two or more hydroxyl groups in the molecule (p. 575). The mordants are salts of insoluble hydroxides, such as those of aluminum, chromium, or iron. They are either salts of a weak acid, for example, aluminum acetate, or basic salts of a strong acid, for example, basic aluminum sulfate. The metallic ions form insoluble lakes with the dye, and these are precipitated in or adsorbed by the fiber. Heating usually is necessary.

Turkey red is the best known color obtained from alizarin. The mordant is a suitable aluminum salt. The original dull color is made a bright red by treatment with Turkey red oil, a sulfated castor oil from castor oil and sulfuric acid, or, better, by treatment with a solution of a soluble salt (sodium or ammonium) of the oil. The final step is treatment with a solution of calcium acetate, followed by steaming.

Vat dyes are reduced under alkaline conditions to compounds related to anthrahydroquinone (p. 573), and these dissolve under basic conditions. After absorption by the fiber, the reduced forms are reoxidized to the original dye.

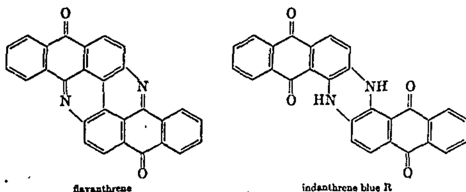
Algol Yellow WG, 1-Benzamidoanthraquinone. This is one of the simpler anthraquinone vat dyes. *It is obtained from 1-aminoanthraquinone* by the action of benzoyl chloride in a boiling nitrobenzene solution. Aminoanthraquinone can be obtained from anthraquinone-1-sulfonic acid (p. 574),

or from 1-chloroanthraquinone (p. 570) by autoclaving with aqueous ammonia. *Algol yellow WG* is a yellow, insoluble dye, and in contact with a weakly alkaline solution of sodium hydrosulfite it is converted into the soluble sodium salt of the reduced form, the "vat." This reduced form is converted by oxygen into the original algol yellow.



Two dyes that are much more valuable are indanthrene red 5 GK (algol red), 1,4-dibenzamidoanthraquinone, and indanthrene yellow GK, 1,5-dibenzamidoanthraquinone. The former results from the sodium sulfide reduction of 1-amino- -nitroanthraquinone, which can be obtained from 1-aminoanthraquinone by nitration of the proper N-acyl derivative (anthraquinoyloxamic acid). The latter is prepared from 1,5-dinitroanthraquinone by reduction with sodium sulfide. The respective diamino anthraquinones are benzoylated to yield the respective dyes.

Flavanthrene (Flavanthrone) and Indanthrene Blue R. These valuable fast dyes are examples of more complicated vat dyes.



Flavanthrene is obtained from 2-aminoanthraquinone by the action of antimony pentachloride, or by fusion with potassium hydroxide at 330 to 350° in the presence of an oxidizing agent. Indanthrene blue is formed from β-aminoanthraquinone by heating it with potassium hydroxide and potassium nitrate at 200°.

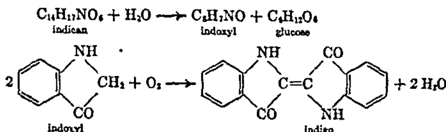
THE INDIGOIDS

Two indigoid dyestuffs have been known since ancient times, *viz.*, indigo, a blue dye, and Tyrian purple, a purple dye. Indigo can be obtained from a number of plants, among them woad (*Isatis tinctoria*), formerly grown in many European countries, and members of the genus *Indigofera*, formerly

grown in India for the production of indigo. Tyrian purple can be obtained from the purple snail, found along the shores of the Mediterranean Sea (p. 718).

Indigo, Indigotin, $C_{16}H_{10}O_2N_2$. Of all dyes, natural or synthetic, this is still one of the most important, if not the most important. It is present in the plants just mentioned as **indican,** a glucoside of indoxyl (p. 670). This is extracted from the plant with water. Hydrolysis, promoted by the enzymes of the plant, gives indoxyl, and this is oxidized by the oxygen of the air to indigo.

$$\underset{\text{indican}}{C_{14}H_{17}NO_6} + H_2O \longrightarrow \underset{\text{indoxyl}}{C_8H_7NO} + \underset{\text{glucose}}{C_6H_{12}O_6}$$



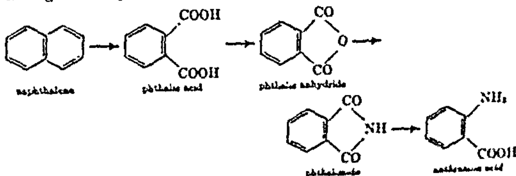
Natural indigo prepared in this way is not a pure substance, for it is contaminated by small amounts of other substances, among them indigo red and indigo brown. Indigotin is a dark blue solid insoluble in water, alcohol, ether, and most common solvents, slightly soluble in aniline, from which it can be crystallized. Oxidizing agents (nitric acid, dichromic acid) attack indigotin, with formation of isatin (p. 670).

The structure of indigo was established by Baeyer in 1882. As written above, the molecule is not symmetrical about the double bond. Formerly, it was so written, with the two carbonyl groups on the same side of the double bond. The older formula is the *cis*-form, the newer, the *trans*-form. The chromophore group,

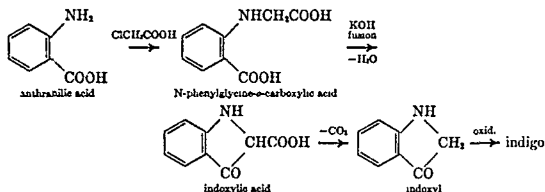


consists of two carbonyl groups that are conjugated through the vinylene group.

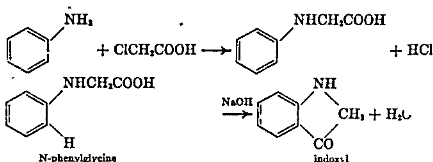
An important industrial process was developed in 1897 in Germany from anthranilic acid. The production of this from naphthalene through phthalic anhydride and phthalimide became economical through the discovery that naphthalene can be oxidized to phthalic acid with fuming sulfuric acid containing a mercury salt, which acts as a catalyst.



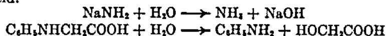
Anthranilic acid is converted to N-phenylglycine-*o*-carboxylic acid with chloroacetic acid, then to indoxylic acid by fusion with potassium hydroxide and this, by loss of carbon dioxide, to indoxyl. Oxidation of indoxyl yields indigo, as already described.



A simpler method, and the one by which indigo is now largely produced, involves the condensation of aniline with chloroacetic acid to N-phenylglycine, the conversion of this by fusion with sodium hydroxide and sodamide to indoxyl, and the oxidation of the latter by oxygen to indigo.

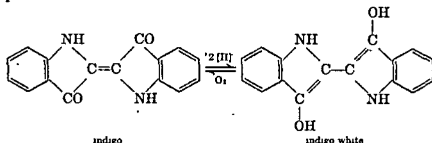


Sodamide is needed to react with the water formed, for this, under the strongly alkaline conditions, would cause scission of N-phenylglycine to aniline and glycolic acid.



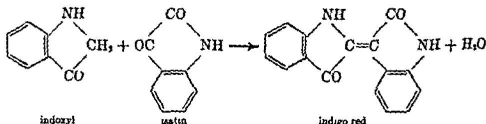
$$NaNH_2 + H_2O \longrightarrow NH_3 + NaOH$$
$$C_6H_5NHCH_2COOH + H_2O \longrightarrow C_6H_5NH_2 + HOCH_2COOH$$

Dyeing with indigo is accomplished by reducing the dye, under alkaline conditions to "indigo white," an almost colorless dihydroxy compound that has the properties of a weak acid.

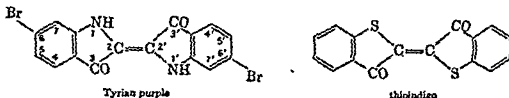


The usual reducing agent is sodium hydrosulfite or sodium sulfoxalate formaldehyde (p. 704). Other reducing agents that may be used are stannous salts, ferrous salts, or reducing sugars. In earlier times reduction was brought about by bacteria that are naturally present in bran or in plants such as woad and madder Indigo is regenerated within the fiber by exposure to oxygen, or by the action of a suitable oxidizing agent.

Indigo Red. This is present in crude natural indigo. It has little practical value. It can be prepared artificially from indoxyl and isatin.

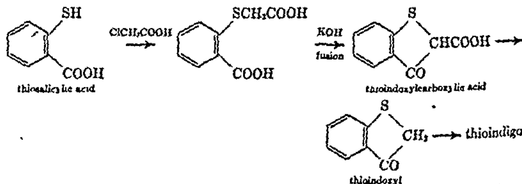


Numerous derivatives of indigo are known, such as thioindigo (Ciba red), and many halogen derivatives, among them, Tyrian purple, 6,6'-dibromoindigo.



Tyrian purple occurs naturally in the purple snail, *Murex brandaris.* It takes eight or nine thousand snails to yield a gram of the dye. This explains its rarity and why the color of purple came to be the symbol of royalty in former times. The dye is no longer of commercial value.

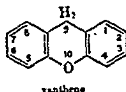
Thioindigo (thioindigo red B) is a valuable vat dye. It can be synthesized in different ways. In one method thiosalicylic acid is the starting material, the steps being analogous to those in the synthesis of indigo from anthranilic acid.



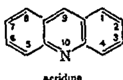
XANTHENE AND OTHER DYES

There are numerous dyes in which two benzene rings are fused with a heterocyclic ring system. Among these are the xanthene dyes (related to xanthene), acridine dyes (derivatives of acridine), phenazine dyes (deriva-

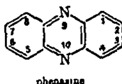
tives of phenazine), and thiazine dyes (related to phenothiazine). The numbering is taken from *Chemical Abstracts.*



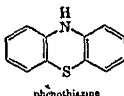
xanthene



acridine

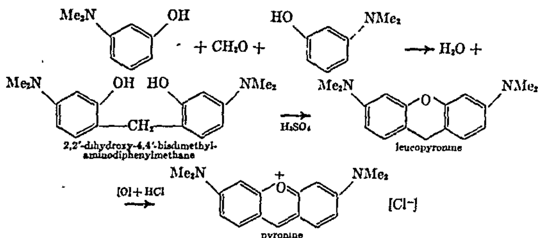


phenazine



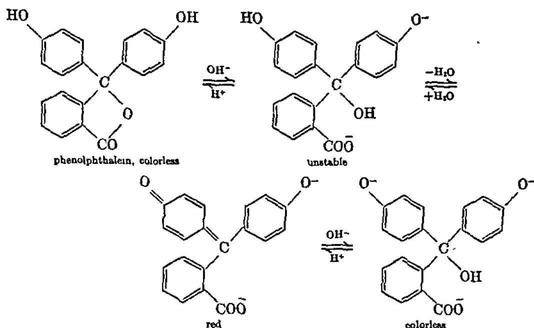
phenothiazine

Pyronine. This is one of the simplest of the dyes of the xanthene group. Its formation, by the condensation of formaldehyde with N,N′-dimethyl-*m*-aminophenol illustrates a general method for the preparation of pyronine (basic) dyes. The first product, 2,2′-dihydroxy-4,4′-bisdimethylaminodiphenylmethane, undergoes cyclization with sulfuric acid to yield leucopyronine. Oxidation of this under acidic conditions yields pyronine.



As in the case of many other dyes, the intense color of pyronine can be ascribed to the distribution of the positive charge among the oxygen and nitrogen atoms, as the result of resonance. Wool and silk are dyed red, with a yellow fluorescence, but the color is not very fast to light. Derivatives, for example, the rhodamines, are better dyes (p. 721).

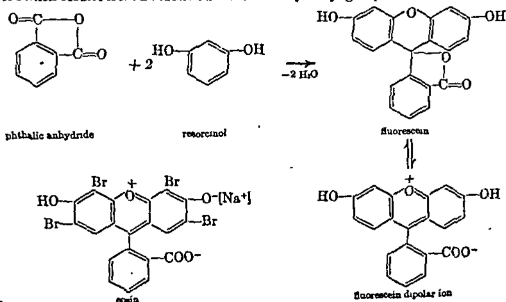
Phenolphthalein. This is not a xanthene color, because it lacks the heterocyclic ring. It is classified as a phthalein. It is mentioned here, however, because the reaction of its formation is similar to the reaction by which a number of xanthene dyes are prepared. Phenolphthalein is formed in a reaction between phthalic anhydride and phenol when they are heated at 150–180° with a suitable catalyst (zinc chloride or sulfuric acid, p. 501). Phenolphthalein is a colorless solid, insoluble in water, but it dissolves in aqueous alkali with a red color. Addition of excess alkali causes a fading of the color. The changes are shown by the formulas on the next page.



Alkali opens the lactone ring and forms a salt at one phenolic group. It is convenient to show the reaction in steps, with the formation of a hypothetical unstable intermediate that changes to a colored ion. The intense color here is ascribed to resonance which places the negative charge on either of two equivalent oxygen atoms. Excess alkali, by salt formation at the second hydroxyl group destroys the color, since resonance involving migration of the charge is no longer possible.

Phenolphthalein is a valuable indicator. In dilute aqueous solution the change is from colorless to pink, *p*H range 8 to 10. Phenolphthalein has a mild laxative action.

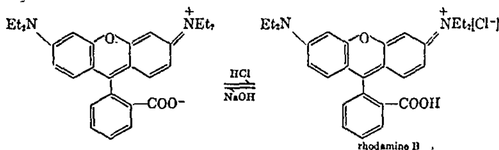
Fluorescein. This is obtained by heating phthalic anhydride and resorcinol at 200 to 205° for about a day. The reaction is somewhat similar to the one by which phenolphthalein is formed and is characteristic of *m*-dihydric phenols. Pyrone ring formation results from a reaction between two hydroxyl groups.



Fluorescein can be obtained as orange colored crystals. It is insoluble in water, but dissolves in alkalies to give a reddish solution showing a strong, beautiful green fluorescence. The sodium (or potassium) salt is called **uranin.** The color of the solid is ascribed to its dipolar ion structure. Other resonance forms can be written with the positive charge located on one of the other two oxygen atoms. Fuorescein dyes silk and wool a yellow shade but the color is fugitive. Therefore fluorescein is of no value as a dye. However, some derivatives are dyes, for example, eosin, and other halogenated derivatives.

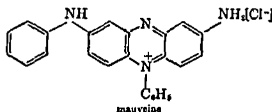
Tetrabromofluorescein. This is obtained by brominating fluorescein in glacial acetic acid. It is a garnet red solid, insoluble in water, soluble in alcohol. Its sodium salt, **eosin,** is soluble in water and dyes silk and wool a brilliant red. Some red inks are made with eosin.

Rhodamine B. This is an example of a number of dyes. It is made from N,N-diethyl-*m*-aminophenol and phthalic anhydride. The dye is the hydrochloride salt.



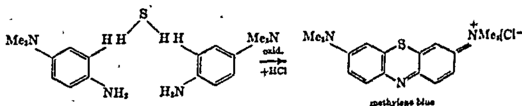
This dyes silk and wool a strongly fluorescent bluish red.

Mauveine (Perkin's mauve). This was the first synthetic dye (Wm. H. Perkin, 1856). Perkin's mauve was a mixture, but the main component was mauveine. Four molecules of aniline are involved in its preparation.



The dye is of historical interest mainly (p. 608), for it has little practical value. It is an example of the phenazine group of dyes, among which are many good ones.

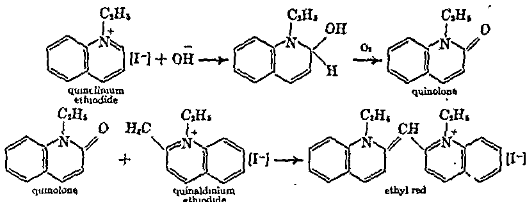
Methylene Blue. This is one of the best known of the thiazine dyes. It is used as a dye and also for biological staining. It is made from *p*-amino-N,N-dimethylaniline, hydrogen sulfide, and ferric chloride. The last acts as an oxidizing agent.



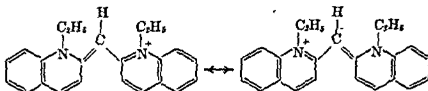
QUINOLINE DYES

Among the dyes derived from quinoline are the cyanine dyes, extensively employed for sensitizing photographic plates to the colors that ordinarily would have little or no effect without sensitization. The violet end of the *spectrum has the greatest effect on photographic emulsion, the red end the* least. General methods of preparation of the cyanine dyes are condensation under basic conditions of: (1) a quinolinium alkyl iodide with a quinaldinium or lepidinium alkyl iodide, and (2) a quinaldinium or lipidinium alkyl iodide with chloroform or ethyl orthoformate, or other suitable compound. (Quinaldine is 2-methylquinoline, lipidine is 4-methyl quinoline.)

Ethyl Red. *This illustrates the first method of preparation.* Quinolinium ethiodide, quinaldinium ethiodide, and potassium hydroxide are heated in ethanol and in contact with the air.

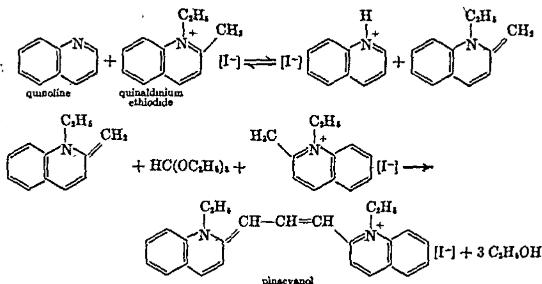


Ethyl red sensitizes to the green, yellow, and orange parts of the spectrum. Ethyl red is a resonance hybrid. The distribution of the positive charge of the cation, shown below for two of the resonance forms, is the cause of the intense color.



Pinacyanol. This is a blue dye sensitizing the photographic plate to the yellow, orange, and red. It is made by heating quinaldinium ethiodide, ethyl orthoformate, and quinoline (the solvent). Quinoline also serves as a base. It is believed to initiate the reaction by removal of the elements of hydrogen iodide from some of the quinaldinium salt, to form a reactive intermediate, a

gated chain, in comparison to that of ethyl red, causes a shift in the absorption band towards the red end of the spectrum.

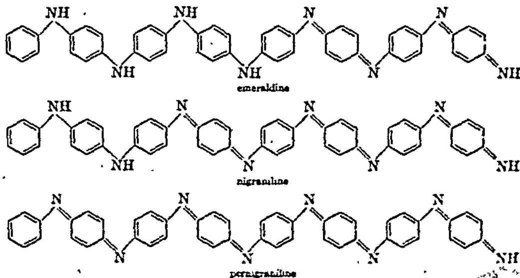


Ethyl red, pinacyanol, and other similar dyes are used in the manufacture of orthochromatic plates and films, *i.e.*, those sensitized to the visible spectrum. More complicated dyes sensitize to the infrared, some as far out as 13,000 Å. These have a longer conjugated chain between nitrogen atoms. Some have other heterocyclic systems in place of quinoline.

MISCELLANEOUS COLORS

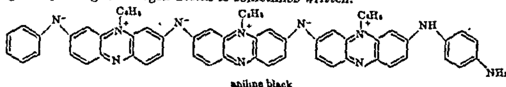
Aniline Black. When an aniline salt is oxidized by a variety of oxidizing agents (dichromate, chlorate, ferric salts), the important black dye, aniline black, is obtained. Usually it is produced directly on the fiber. With chlorate, a catalyst is necessary in order that the oxidation proceed as desired; it may be a copper or vanadium salt.

The oxidation proceeds through blue intermediates to the final product. Oxidation in the cold gives first emeraldine (blue, forming green salts), then nigraniline (dark blue, forming blue salts), and finally pernigraniline. These are all sensitive to acids. Since they fade easily, they are not satisfactory dyes. They are mixtures.



Emeraldine has two quinonediimine rings; nigraniline, three; and pernigraniline, four. These are the chromophore groups.

lation is carried out hot.
, with formation of three
phenazine rings A dipolar ion structure having three positively charged and three negatively charged nitrogen atoms is sometimes written.



aniline black

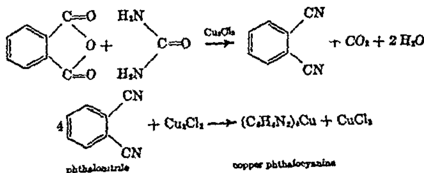
This, however, should be regarded as only one of the many resonance forms. One resonance form resembles pernigraniline in the alternate arrangement of single and double bonds, with the exception of the right hand unit. The molecular weight of aniline black is not known; consequently the structure may be more complex. Aniline black is a remarkably fast dye and one of the most important blacks.

Sulfide Colors. A rather large number of important dyes are produced by the fusion of an aromatic compound with sulfur or with sodium polysulfides. Different types of organic compounds may be used, for example, amines, phenols, and nitro compounds. Complex reactions take place. The structures of some sulfur dyes are known, but many are not. However, sulfur is always present in the molecule, usually as a disulfide linkage, sometimes as a sulfide linkage, or as a member of a heterocyclic ring.

Dyeing with sulfur colors is usually carried out by first dissolving the insoluble dye in a basic solution of sodium sulfide, or sometimes sodium hydrosulfite, whereby the dye is reduced to its leuco form. Generally this involves reduction of a disulfide linkage to two acidic thiol groups which can react with bases to form salts. After the fabric has been impregnated with the leuco compound, it is exposed to air or to the action of an oxidizing agent, with regeneration of the color within the fabric. The process is much like vat dyeing. Many sulfide colors are remarkably fast. They include yellows, browns, greens, blues, and blacks. On account of their cheapness they are used extensively.

Phthalocyanines. These are metallic complexes of phthalocyanine with metallic ions. They are remarkably stable, highly colored solids, much prized as pigments.

Copper phthalocyanine (Fig. 40) is obtained by heating at 195° in a suitable solvent (1,2,4-trichlorobenzene) phthalic anhydride, urea, and cuprous chloride, along with a small amount of ammonium molybdate. Yields are good (*ca.* 75%). Phthalonitrile is considered to be an intermediate.



Phthalonitrile or other *o*-dinitrile, or any compound or combination of substances that gives an *o*-dinitrile on heating, will yield a phthalocyanine when heated with a suitable metal or a suitable metallic salt. The copper salt is a violet-blue powder, of

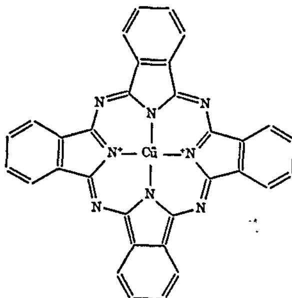


Figure 40 • Copper Phthalocyanine

remarkable stability. It is insoluble in water and in the usual organic solvents and is very fast towards light. It is not altered by hot aqueous acids or alkalis, nor by concentrated sulfuric acid, in which it is soluble. At about 600° and under reduced pressure it can be sublimed unaltered.

Structurally phthalocyanine is much like protoporphyrin (Fig. 38, p. 668) except that *phthalocyanine has four nitrogen atoms in place of the four methine groups of* protoporphyrin, and four benzene rings fused to the pyrrole rings, whereas in protoporphyrin there are eight side chains.

PROBLEMS

1. Write the structural formula of the product to be expected as the result of monobromination and dibromination of the following:

a) aniline yellow
b) butter yellow
c) methyl orange
d) methyl red
e) Sudan III
f) auramine O
g) malachite green
h) brilliant green
i) pararosaniline
j) crystal violet
k) ethyl purple
l) algol yellow
m) phenolphthalein
n) fluorescein

2. *Show how the following may be synthesized from substances that are simpler in structure than anthracene and are available in quantity from coal tar or bone oil.*

a) naphthol yellow S
b) gambine
c) aniline yellow
d) Bismarck brown
e) methyl orange
f) methyl red

g) para red
h) Congo red
i) Sudan III
j) malachite green
k) brilliant green
l) pararosaniline
m) crystal violet
n) aniline blue
o) alizarin
p) algol yellow
q) algol red
r) indanthrene yellow GK
s) flavanthrene
t) indanthrene blue
u) Tyrian purple
v) pyronine
w) phenolphthalein
x) ethyl red
y) pinacyanol
z) copper phthalocyanine

3. Show how to account, in terms of resonance, for the way in which the presence of an auxochrome group intensifies the color of a chromogen, as exemplified by:

a) aniline yellow
b) butter yellow
c) para red
d) Congo red
e) Sudan III
f) benzopurpurin 4B

4. Show how the intense color of the following may be accounted for in terms of resonance:

a) brilliant green
b) pararosaniline
c) aniline blue
d) alizarin
e) algol yellow
f) flavanthrene
g) indanthrene blue
h) indigo
i) Tyrian purple
j) thioindigo
k) fluorescein
l) mauveine
m) emeraldine
n) nigraniline
o) pernigraniline
p) copper phthalocyanine

5. Write a structure for aniline black similar to the one assigned to pernigraniline.

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